Stereoselective routes to the total synthesis of the polyene macrolide viridenomycin

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A thesis submitted to the University of Durham for the degree of Doctor of Philosophy.

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PREFACE

To the best of my knowledge, the research described in this thesis is entirely original except where due reference is made, and has not been previously submitted in support of an application for another degree or qualification at this or any other university or institute of learning.

The introduction to this thesis was written by C.E. Thirsk but was published in a slightly modified form under the name of C.E. Thirsk and A. Whiting.

C. E. Thirsk

Durham, January 2003.

Contents

Acknowledgements

First, I would like to express sincere thanks to my supervisor Dr Andy Whiting for his advice, encouragement, and support over the last three years I have been a member of his research group.

Thanks are also due to my industrial supervisor Dr Graham Maw, both for the different perspective he lent to the project, and also for the often invaluable advice he proffered.

Special thanks go to all the members of the Whiting group past and present, research students, post-doctoral research assistants, and even some of the memorable young sojourners we were fortunate to have, all of whom made G104/5 (UMIST) and CG115 (Durham) a lively, friendly and thoroughly pleasant environment to work in. It would be remiss not to mention a few of these people, so in particular, my fellow travellers on this long road, David Jay and Hayley Wan (Drs!); special appreciation is also given to Dr Len Patrick, Dr Nadia Suliman, Dr John Hamlin, Dr Allen Bowden, Dr John Hannan and Dr Paul Mather for their wit and sagacity, but mostly for the sheer entertainment! Many thanks also to Chris Murray, Richard Giles, Alex Blatch, Steve Twiddle, Mike Probert, John Henry, Abass Bundu and young Sam Coghlan, for the friendship and laughter!

None of this research would have been possible without the technical staff at UMIST and Durham; special thanks go to the NMR staff at Durham for the excellent service they provide, and also to the Durham glassblowers for their craftsmanship, prompt delivery, and understanding ears!

Last, but by no means least, a big thank-you to all my family who have supported me through these last three years, and indeed, throughout the duration of my higher education which has now spanned some eight years. Without them, for all sorts of reasons too numerous to list here, none of this would have been possible and this thesis would certainly bear somebody else's name.

Abstract

Viridenomycin **11** is a polyene macrolide possessing a wealth of biological activity. As part of an ongoing program examining the stereoselective synthesis of polyene natural products, a strategy was explored to effect the total synthesis of viridenomycin **11**.

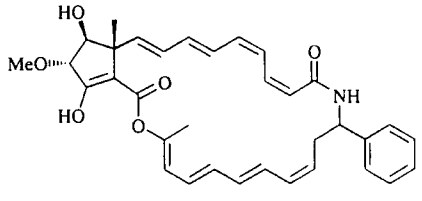
As a consequence of the adopted retrosynthetic strategy, the project was naturally divided into three main areas: efforts directed towards the southern (*E*, *E*, *E*, *Z*)-tetraene **210**, towards the northern (*E*, *Z*, *Z*)-triene **209**, and towards the core cyclopentenone **211**.

Both polyenic sections **209** and **210** were tackled with a view to utilizing palladium-coupling methodology developed in the group, whereby vinylboronates of type **122** undergo Heck coupling with alkenyl halides, affording polyenyl boronates that may then be converted into polyenyl iodides *via* stereoselective iodo-deboronation. The geometry of the new double bond is determined by the order of reagent addition during the iodo-deboronation. Vinylboronates such as **122** may thus be regarded as a vinyl dianion equivalent, permitting ready access to either alkene geometry, and allowing a polyene chain to be built up *via* an iterative process.

Efforts towards **209** gave rise to a surprising reaction, in which it was discovered that iodoacrylates **214** are problematic Heck coupling partners due to a propensity to undergo novel Michael addition-elimination reactions with most amine bases, instead affording amino acrylates in excellent yields.

Efforts towards **210** called for the development of new and robust methods for the elaboration of the amino acid phenylglycine, providing greatly improved procedures for its conversion to the corresponding *N*-protected β-amino alcohol, *N*-protected β amino-*O*-sulfonylates, *N*-protected β-amino iodides and *N*-protected β-amino nitriles, all valuable synthetic intermediates in their own right. An advanced synthon *en route* to **210** was prepared by Heck coupling of (*Z*)-iodide **214** with vinylboronate **272**, representing a considerable in-road into the synthesis of this fragment.

Markedly different chemistry was required to synthesize **211**. Its retrosynthetic strategy called for a stereoselective aldol reaction, and as a consequence of this work it was found that novel oxazaborolidinone mediated Mukaiyama aldol additions between diene 4-(*tert*-butoxy)-2,4-bis[(trimethylsilyl)oxy]-1,3-butadienyl methyl ether **335** and a wide range of electrophiles gave aldol products in isolated yields of up to 90%.



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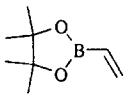

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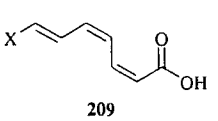

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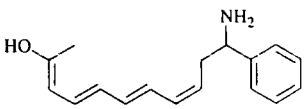

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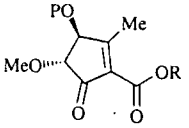

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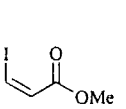

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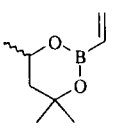

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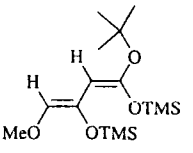


335

Abbreviations

:**C** or :**H**	implies double bond to either C or H.
aq.	aqueous.
asymm.	asymmetric.
b	broad.
bs	broad singlet.
BOC	*tert*-butoxycarbonyl.
BOX	bis(oxazolinyl)
Bu	*n*-butyl.
cat.	catalytic.
CBH	catecholborane.
CI	chemical ionization.
conj.	conjugated.
Cp	cyclopentadienyl.
Cq	quaternary carbon.
dba	dibenzylidene acetone.
DBU	1,5-diazabicyclo[4.3.0]undec-7-ene.
DCC	1,3-dicyclohexylcarbodiimide.
DCM	dichloromethane.
dd	double doublet.
de	diastereomeric excess
DEAD	diethylazodicarboxylate.
def.	deformation.
DIBAL-H	diisobutylaluminium hydride.
DMAP	4-dimethylaminopyridine.
DMF	*N*,*N*'-dimethylformamide.
DMI	1,3-dimethylimidazolidin-2-one.
dppb	1,4-bis(diphenylphosphino)butane.
dppe	1,2-bis(diphenylphosphino)ethane.
dppf	bis(diphenylphosphino)ferrocene.
DPM	diphenylmethyl.
dppp	1,3-bis(diphenylphosphino)propane.
EDA	ethylenediamine.
ee	enantiomeric excess
ES^+	electrospray (positive ion).

Et	ethyl.
EtCN	propionitrile.
EtOAc	ethyl acetate.
Et_2O	diethyl ether.
Hal	Halogen
HMDS	hexamethyldisilazide.
HMPA	hexamethylphosphoramide.
$IPCBH_2$	monoisopinocampheylborane.
iPr	isopropyl.
KHMDS	potassium bis(trimethylsilyl)amide.
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide.
m	multiplet.
Mbs	methoxybenzenesulfonyl.
Me	methyl.
MeCN	acetonitrile.
MEM	β-methoxyethoxymethyl.
Ms	mesyl, methanesulfonyl.
NaHMDS	sodium bis(trimethylsilyl)amide.
n-Bu	*n*-butyl.
NOBIN	2-hydroxy-2'-amino-1,1'-binaphthyl
NMR	nuclear magnetic resonance.
Ns	nosyl, 4-nitrobenzenesulfonyl.
P	in a scheme, represents a protecting group.
PBH	pinacolborane.
PCC	pyridinium chlorochromate.
PDC	pyridinium dichromate.
Pet.	petroleum.
Ph	phenyl.
PhMe	toluene.
ppte	precipitate
Pr	*n*-propyl.
Ps	pipsyl, 4-iodobenzenesulfonyl.
PyBOX	[pyridine(bisoxazoline)]
py	pyridine.

q	quartet.
sat.	saturated.
SEM	β-(trimethylsilyl)ethoxymethyl.
str.	stretch.
sym.	symmetric.
t	triplet.
TADDOL	(4*R*, 5*R*)- or (4*S*, 5*S*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol.
TBAB	tetrabutylammonium bromide.
TBACN	tetrabutylammonium cyanide.
TBAI	tetrabutylammonium iodide.
TBAF	tetrabutylammonium fluoride.
TBDMS	*tert*-butyl-dimethylsilyl.
TBDPS	*tert*-butyl-diphenylsilyl.
t-Bu	tertiary butyl.
TEA	triethylamine.
THF	tetrahydrofuran.
TIPS	triisopropylsilyl.
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl.
TOF MS	time-of-flight mass spectrometry.
Ts	tosyl, *p*-toluenesulfonyl.
X	generally taken to mean Cl, Br or I.
XRD	X-Ray Diffraction

1.0 Introduction

Natural products containing conjugated alkenyl units represent a large and structurally diverse group of compounds.[1] Particularly significant are those possessing biological activity, including the eicosanoids (the arachidonic acid derivatives such as the leukotrienes and lipoxins),[2] the retinoids,[3] and the polyene macrolides[4], a large group comprising over 200 members. There are also a considerable number of relatively unexplored polyenes derived from a variety of sources, including marine organisms, fungi, slime-moulds and plants; these polyenes are often produced as a means of chemical defense, and thus also possess potentially useful biological activity.

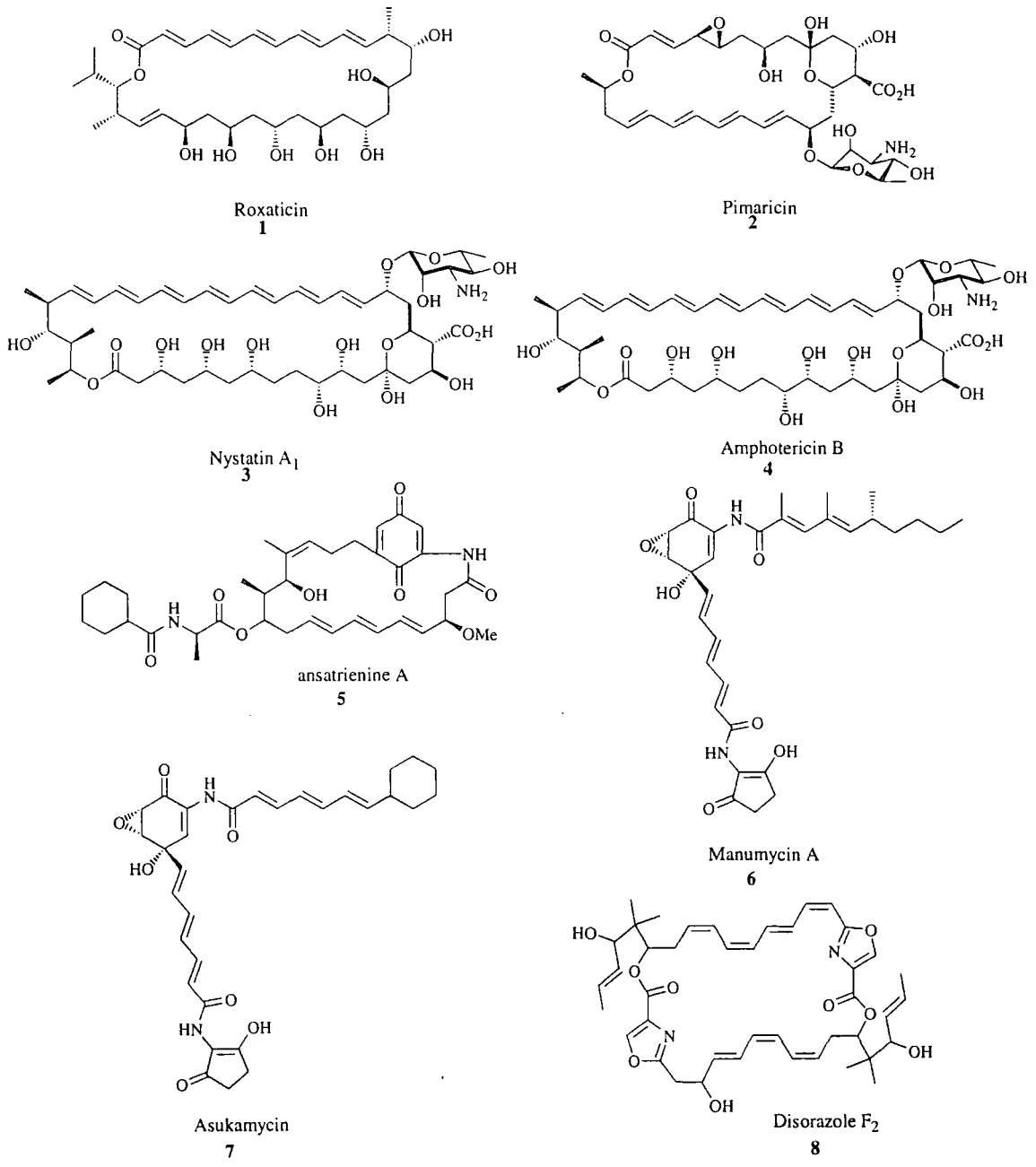
This review covers the literature from 1971 to the present date. It begins with a brief survey of the major sub-categories of polyene natural products, before focussing on methods used to bring about their synthesis. Heavier emphasis will be given to the synthesis of the polyenes themselves and owing to the vast number of natural products containing multiple double bonds, this review will concentrate only on natural products that contain at least a) three all-*trans* conjugated double bonds, or b) *cis*, *cis* or *cis*, *trans* dienyl units.

1.1 Polyenes derived from bacteria

Typically isolated from the *Streptomyces* genera of actinomyces soil bacteria, the polyene and oxo-polyene macrolides[5] are relations of the more familiar macrolide antibiotics (for example, the erythromycins) and represent the most important sub-category of polyene natural products. Structurally, they are very large macrocyclic lactones with 22 to 44 membered rings commonplace. The polyenic section usually incorporates between 4 and 8 conjugated double bonds. Oxo-polyene macrolides such as roxaticin[6] **1** are characterized by having the polyene in conjugation with the lactone linkage (fig. 1). Several members of the polyene macrolide family find service as clinically important anti-fungal drugs, notably pimaricin **2**,[7] nystatin A_1 **3**[8] and amphotericin B **4**,[9] dubbed 'amphoterrible' due to its high nephrotoxicity.

The ansamycin[10] antibiotics are a growing family of *Streptomyces* metabolites, and many of them possess antibacterial, antifungal or antitumour activity. Ansatrienine A (mycotriene) **5**[11] is one of the first isolated examples, and may be taken as a representative member. Also isolated from *Streptomyces sp.*, the manumycins[12,13] (for example, **6** and **7**) are a fairly large and well-studied group of polyenes. This family of antibiotics has attracted considerable attention due to their promising biological activity;

Figure 1

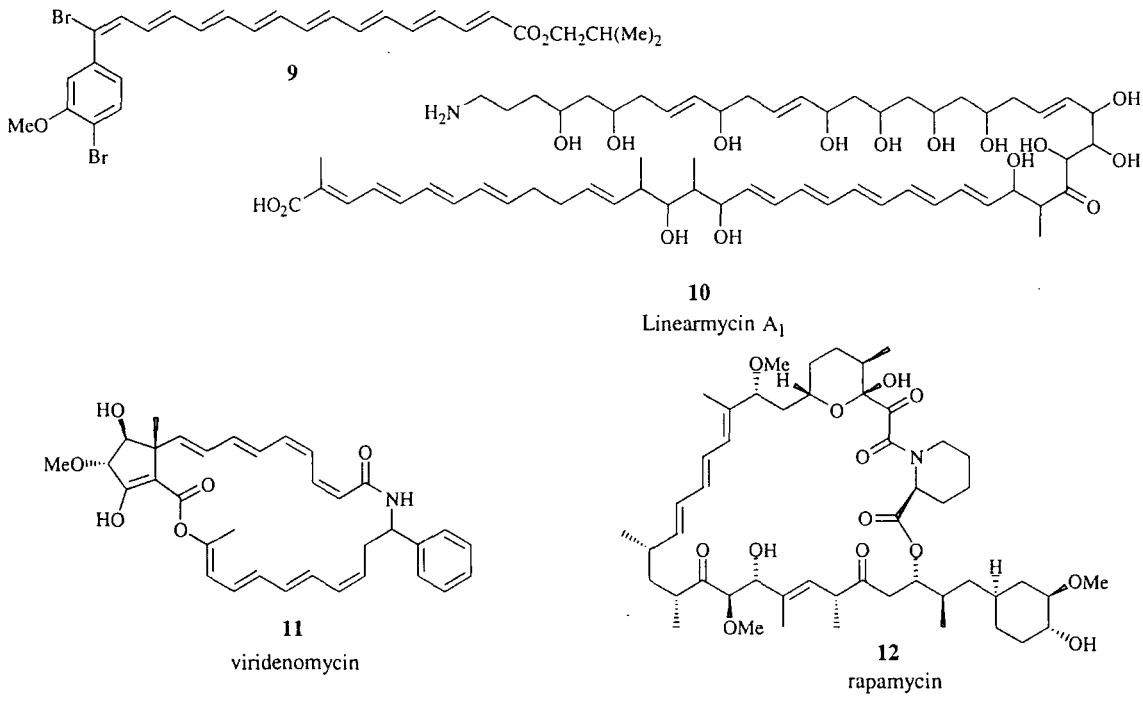


manumycin A **6**, the first to be isolated, shows activity towards fungi and L1210 leukemia stem cells in addition to its antibacterial properties.

Isolated in 1994 from the fermentation broth of the gliding bacteria *Sorangium cellulosum*, the disorazoles,[14] of which disorazole F_2 **8** is typical, are a group of 29 anti-fungal and cytotoxic macrocyclic dilactones. They are all dimer-like, and are differentiated by the positions and stereochemistries of the double bonds, and in the size of, and nature of the substituents on the macrocyclic core.

Aside from these major classes, there are a host of other bacterially derived polyenes (fig 2). Xanthomonadin I **9**, responsible for the vivid yellow colours of *Xanthomonas* colonies, is a rare example of a compound synthesized by a terrestrial organism that

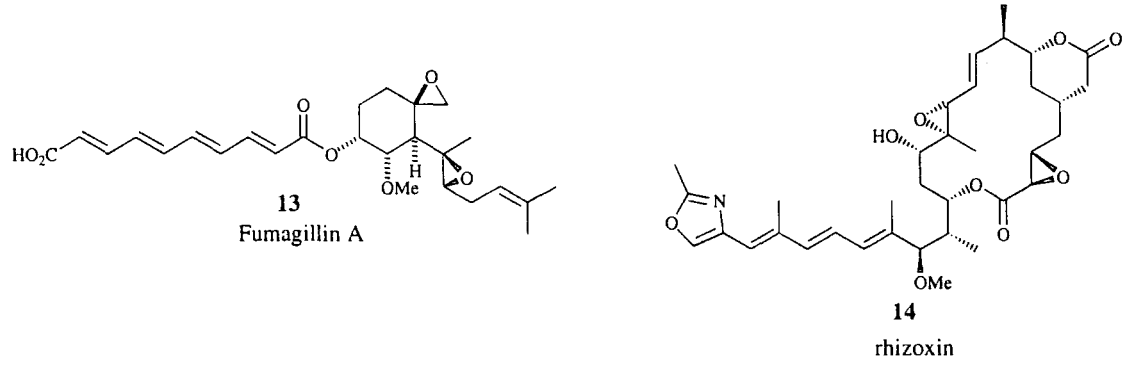
Figure 2



contains bromine.[15] Linearmycin A_1 **10**[16] is an unusually long polyene containing thirteen double bonds, whilst the structurally complex polyenes viridenomycin **11**[17] (an antifungal, antibacterial and antitumour macrolide) and rapamycin **12**[18] (an antibacterial and immunosuppresive agent) are further examples of *Streptomyces* metabolites.

1.2 Polyenes produced by fungi

Figure 3

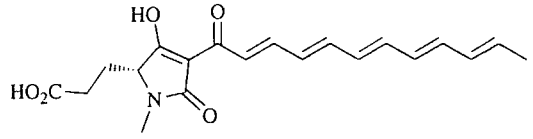


Pigments derived from fungi tend to be of isoprenoidal origin, not arising from the polyketide metabolic pathways that usually give rise to polyenic compounds. There are a few examples however, and a prominent one is that of fumigillin **13**[19, 20] (fig. 3), a

metabolite of *Aspergillus fumigatus* that possesses a wealth of biological activities including amebicidal, anticancer, antiparasitic and antibacterial properties. Also important are the rhizoxins,[21] a family of 16-membered macrolactones isolated from the plant-pathogenic fungus *Rhizopus chinensis.* Rhizoxin **14** is a tubulin binding anti-mitotic agent possessing antifungal and antimicrobial activity in addition to potent *in vitro* cytotoxicity and *in vivo* antitumour activity. It is more potent, yet less toxic than vincristine and has undergone extensive clinical trials. The didesepoxy analogue rhizoxin D[22] has equal potency, but is isolated as a minor component.

1.3 Polyenes derived from slime-moulds and plants

Figure 4



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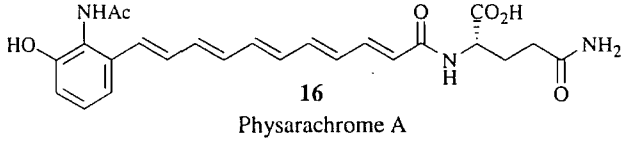
Fuligrobin A



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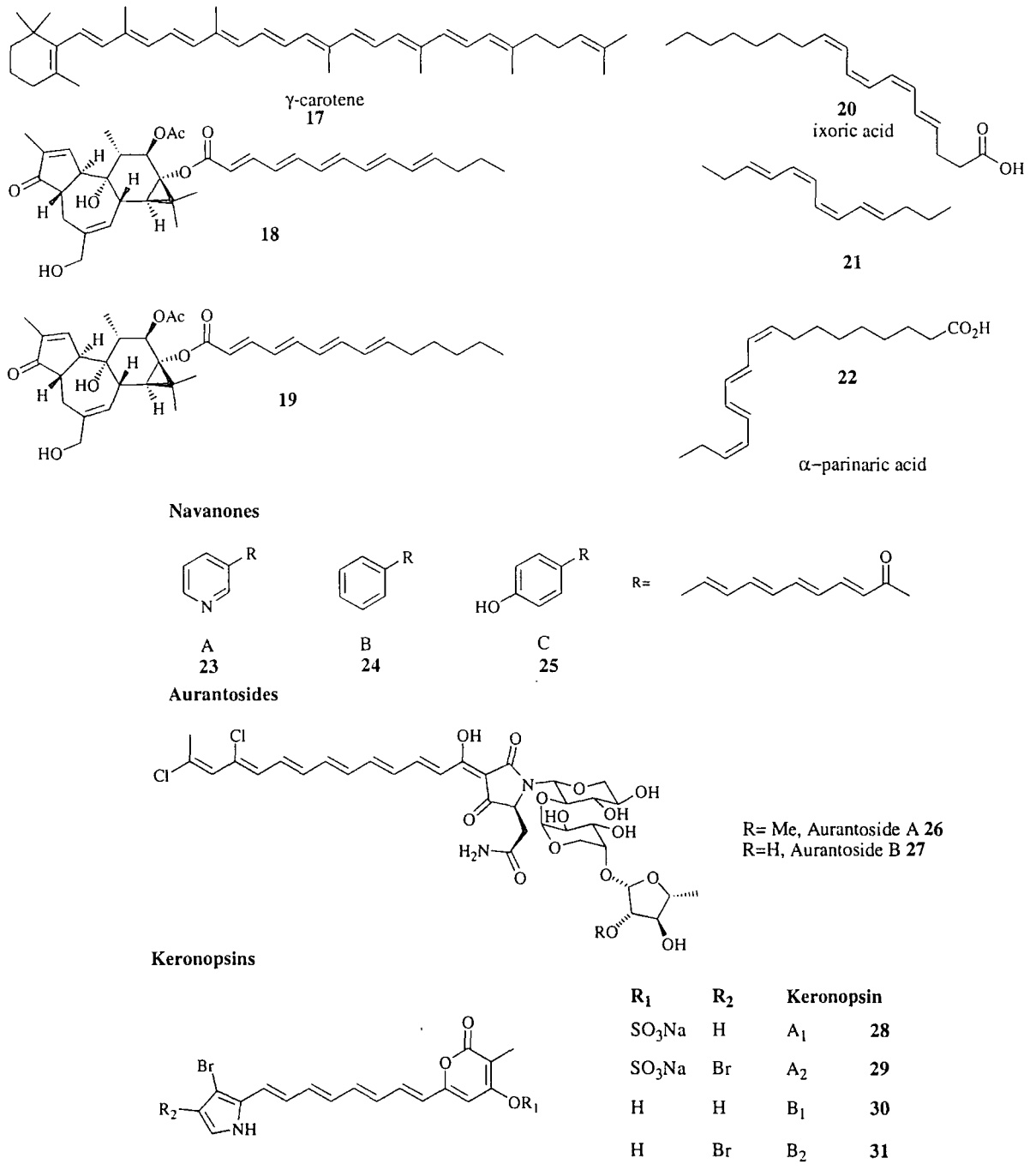
Physarachrome A

Slime moulds, often found amongst moist decaying wood and litter in forests, produce yellow cytotoxic substances such as fuligrobin A **15**[23] and physarachrome A **16**[24] (fig. 4), either as a means of chemical defence, or to function as photoreceptors. Plants synthesize a vast array of polyenic compounds, most familiar of which are the carotenoids[25] (*e.g.* γ-carotene **17**), the most prevalent of all the naturally occuring pigments (fig. 5). The deoxyphorbol ester derivatives **18** and **19** isolated from the caustic sap of the pencil tree, are purported antitumour agents.[26] Also shown are several unusual polyenes containing mixed alkene geometries **20-22**.[27]

1.4 Polyenes derived from marine organisms

Naturally derived polyenes are typically toxic, and often vividly coloured. These two facets are exploited well by many marine organisms which are without the defensive capabilities of many of their larger aquatic cousins.

Figure 5

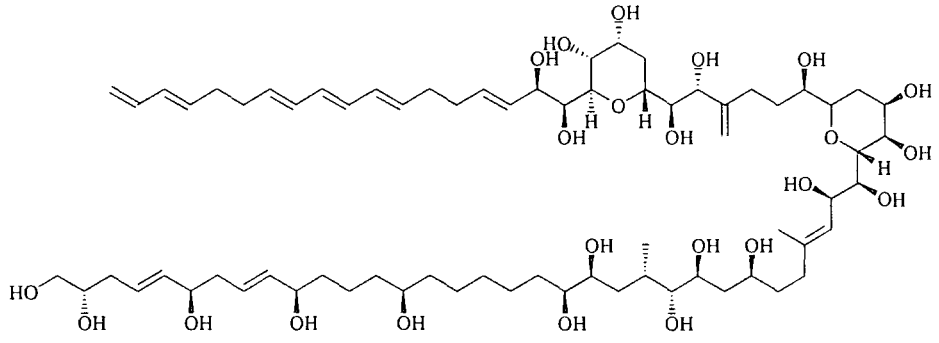


R_1	R_2	Keronopsin	
SO_3Na	H	A_1	**28**
SO_3Na	Br	A_2	**29**
H	H	B_1	**30**
H	Br	B_2	**31**

Opisthobranchia for example, a sub-class comprising the sea-slugs and their allies, lack the protection provided by the hard shell typical of most members of the gastropod class, and secrete brightly coloured polyenic ketones, such as the yellow navanones A-C **23-25** (named after *Navanax inermis*, an ornately coloured sea-slug found off the Californian coast) which act as alarm pheromones.[28] The cytotoxic aurantosides A and B (**26** and **27**, fig. 5), obtained from sponges and isolable as orange amorphous powders, are *N*-trisaccharide tetramic acid derivatives possessing activity against P388 and L1210 leukemia cells.[29a] Aurantosides C[29b] and D-F[29c] have also been recently

isolated and found to possess biological activity. The antibiotic keronopsins **28-31** are produced by *Pseudokeronopsis rubra*, a marine ciliate known for its deep red colour, and are used as chemical weapons against other ciliates and flagellates.[30] Marine dinoflagellates, a type of unicellular aquatic organism possessing both animal and plant characteristics, provide a rich source of structurally diverse natural products with highly specific bioactivity. Certain species produce powerful nerve toxins, and it is these toxins that give rise to the so-called red-tides, formed when the creatures reproduce *en mass* or bloom in shallow waters. The genus *Amphidinium* has been exploited as a source of novel secondary metabolites with unique chemical structures,[31] and amphidinol 3 **32** (fig 6), an antifungal polyene whose structure was recently elucidated,[32] is a prominent example.

Figure 6



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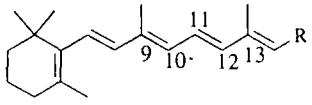
1.5 Polyenes produced by animals

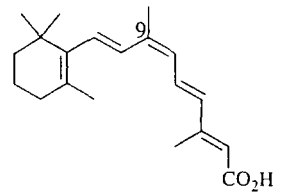
The retinoids[3] **33-37** (fig. 7), a collective term for the various synthetic and natural analogs of retinol (vitamin A) **33**, are vitally important during embryo development and throughout post-natal life in humans. The biological roles they play are dependent both on the nature of the R group and on the geometry of the polyene chain. These factors are the reason that they have been the focus of much synthetic attention, and are often used as the first test of a new polyene-assembling methodology.

Another important group of polyenic biomolecules are the eicosanoids,[2] comprising the structurally related prostaglandins, prostacyclins, thromboxanes and leukotrienes, which are derived from polyunsaturated fatty acids such as arachidonic acid. These compounds are found in minute quantities in most animal cells, and elicit diverse biological responses in most animals. These effects, together with their small, but complex structures, have made them appealing targets for total synthesis; indeed the only means of obtaining sufficient quantities of eicosanoids for evaluation is through chemical synthesis. Lipoxin A **38** (fig 7) possesses similar biological properties to the

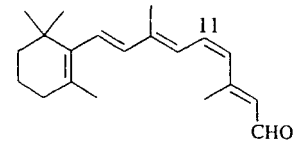
Figure 7



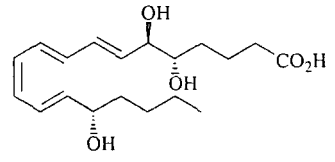
R	name	
CH_2OH	retinol, vitamin A	33
CHO	all-*trans* retinal	34
CO_2H	all-*trans* retinoic acid	35



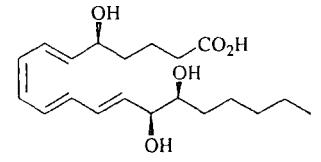
9-*cis*-retinoic acid
36



11-*cis*-retinal
37



Lipoxin A
38



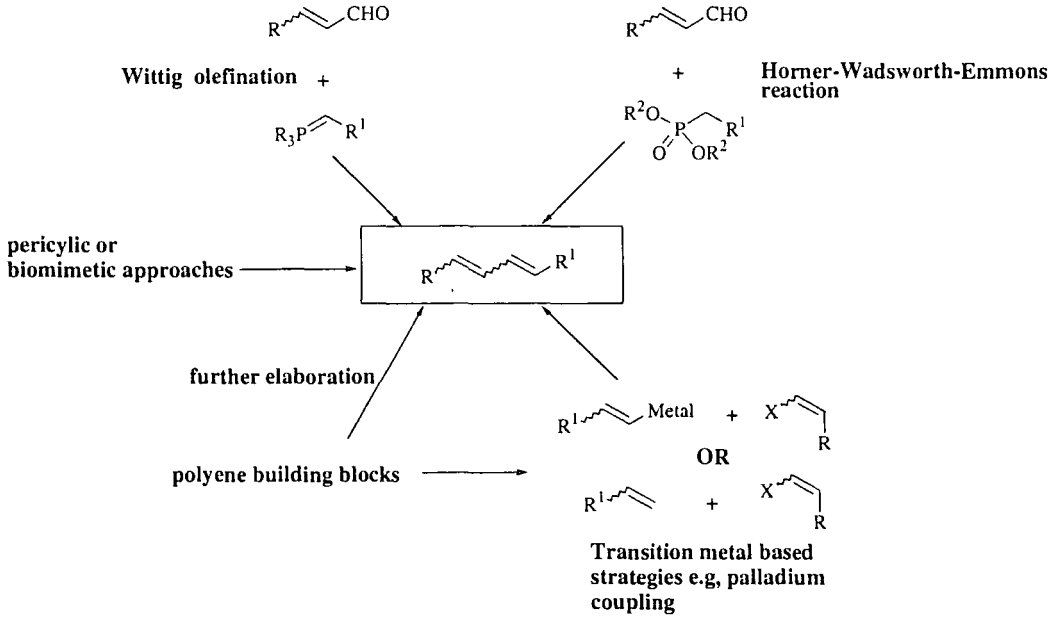
Lipoxin B
39

unstable intermediate leukotriene B_4, and has been synthesized and evaluated biologically.[37]

1.6 Synthesis of polyenes-general strategies

Figure 8 outlines the most common general strategies taken to date in order to access polyenes.

Figure 8



A few fundamental issues need to be considered when synthesizing polyunsaturated compounds. As a general rule, polyenes of the all *trans* nature are more stable than ones containing *cis*-alkenyl units, hence the latter tend to be more difficult to construct, and especially prone to isomerization. Additionally, when a specific isomer is required, as is usually the case, a method that leads to mixtures of *cis*

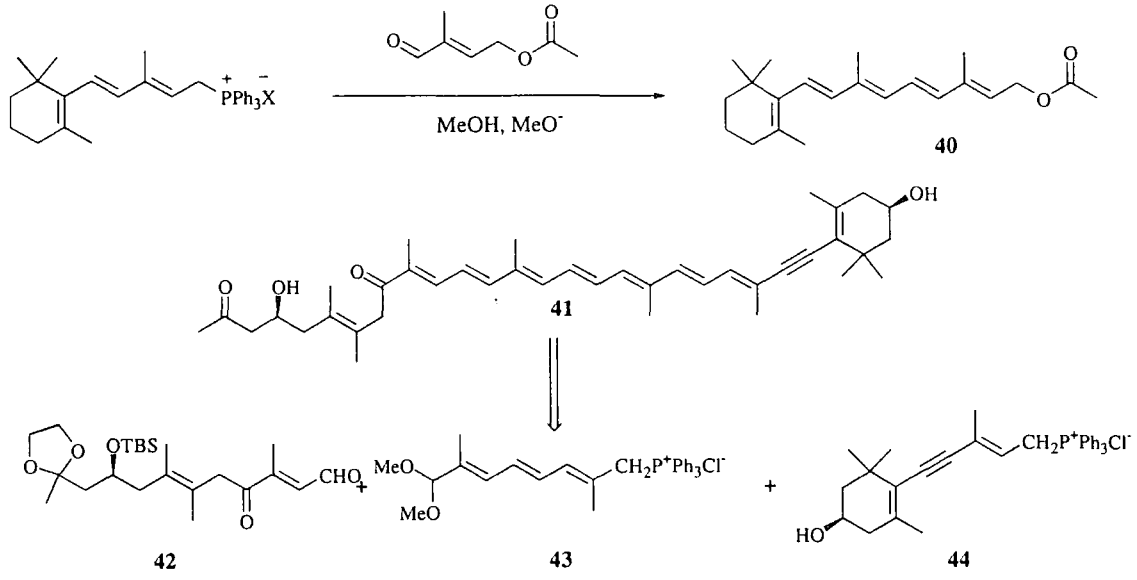
and *trans* isomers will invariably require a tedious and yield-reducing separation, if separation is possible at all.

The principal requirements for polyene synthesis are thus 1) a reliable olefination procedure that produces alkenes in high geometric purity, 2) a procedure that allows ready access to either isomer, whilst at the same time being mild and functional group tolerant.

1.7 Wittig olefination and Horner-Wadsworth-Emmons procedure.

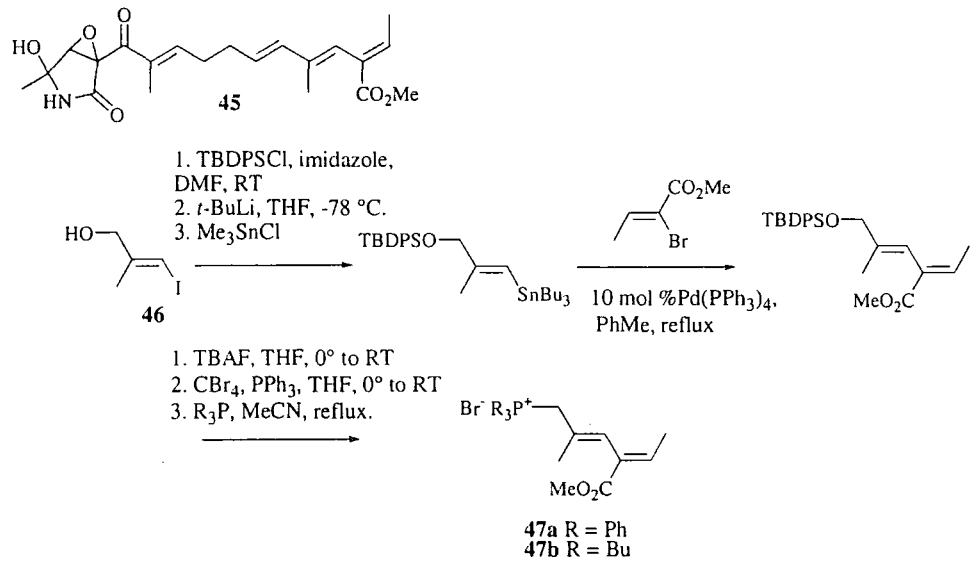
The Wittig reaction[33] has proved historically to be the reaction of choice for the formation of alkenes. It suffers however from a number of disadvantages, the principal one being that it invariably leads to a mixture of isomers, necessitating separation, or isomerization of the unwanted isomer. It also requires preparation of an appropriate ylide, typically requiring a strong base to generate the carbanion, and usually a laborius purification procedure necessary to remove the stoichimetric phosphine oxide by-product. The closely related Horner-Wadsworth-Emmons[34] (HWE) procedure circumvents a number of these problems, and is now increasingly used in all areas of natural product synthesis.

Scheme 1



The BASF synthesis of vitamin A, one of the leading methods of production, utilizes Wittig chemistry on a huge scale to produce the precursor retinyl acetate **40** (scheme 1). A double Wittig reaction was recently employed by Tode's group in the first synthesis of the marine carotenoid crassostreaxanthin B **41** (scheme 1).[35] Condensation of aldehyde **43** with Wittig salts **42** and **44** led to **41** after deprotection. Wittig chemistry was also employed in the synthesis of the side chain of the novel

Scheme 2

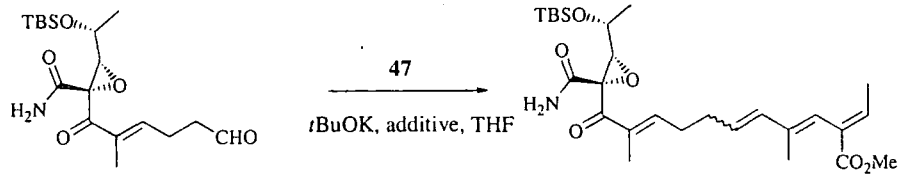


neuritogenic agent epolactaene **45** (scheme 2),[36] with the requisite ylide **47** being prepared in six steps starting from known iodoalcohol **46**. Various conditions were examined in order to give the highest *E/Z* ratio for the Wittig coupling of **47** and **48a** (Table 1); use of the tributylphosphonium salt **47b** gave the highest proportion of the *E* isomer which was separated from the *Z* isomer by flash chromatography.

Table 1: Factors affecting the *E/Z* ratio in the Wittig coupling of 47 and 48a

Ylide	Ylide (equivalents)	Additive	T / °C	E / Z ratio	Yield (%)
47a	2.4	none	-78	---	trace
47a	2.4	18-crown-6 / MeCN	-46	1:1	27
47a	5.0	18-crown-6 / MeCN	-46	1:1	68
47b	5.0	18-crown-6 / MeCN	-46	10:1	69

[a] determined by ^{1}H NMR

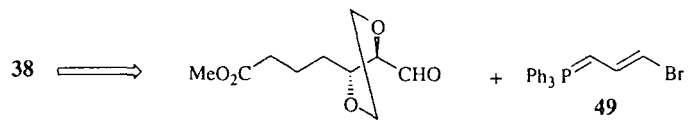


48a **48b**

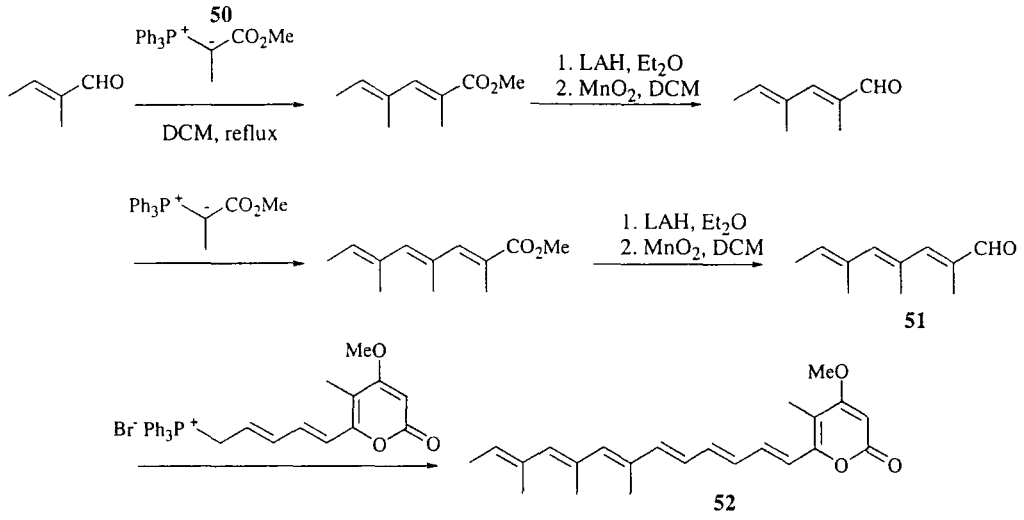
As mentioned previously, arachidonic acid metabolites are important due to their intriguing biological properties, and Yadav and co-workers have developed a convergent synthesis of lipoxin A **38** (scheme 3), with Wittig chemistry being used to install the tetraene portion.

Their synthesis involves a specialized ylide **49**, prepared from propargyl alcohol.[37] In 1991 Pattenden reported the total synthesis of all-*trans* citreomontanin **52**, a hexaene

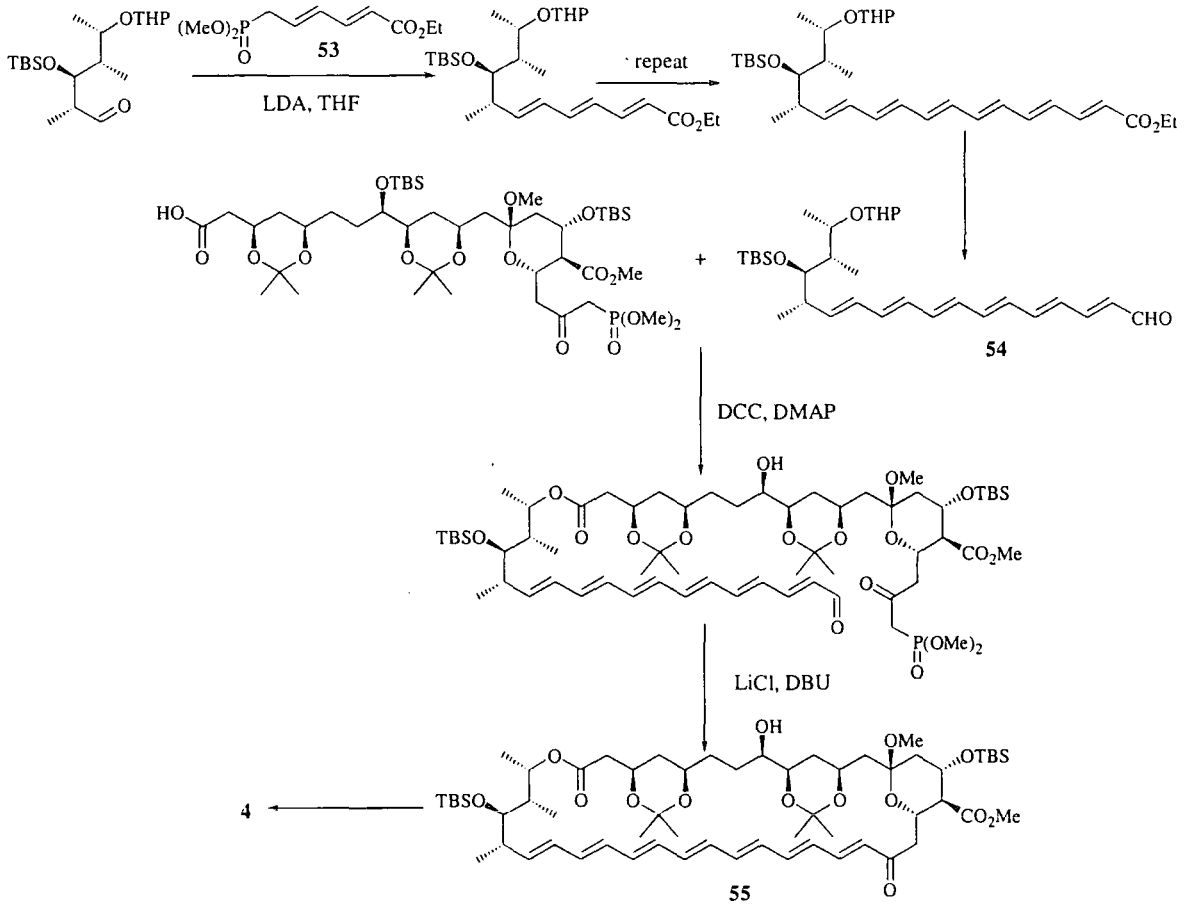
Scheme 3



Scheme 4



Scheme 5



isolated from *Penicillum pedemontanum* and the putative precursor to citreoviridin and citreoviridinol. This was achieved *via* an iterative sequence involving Wittig coupling

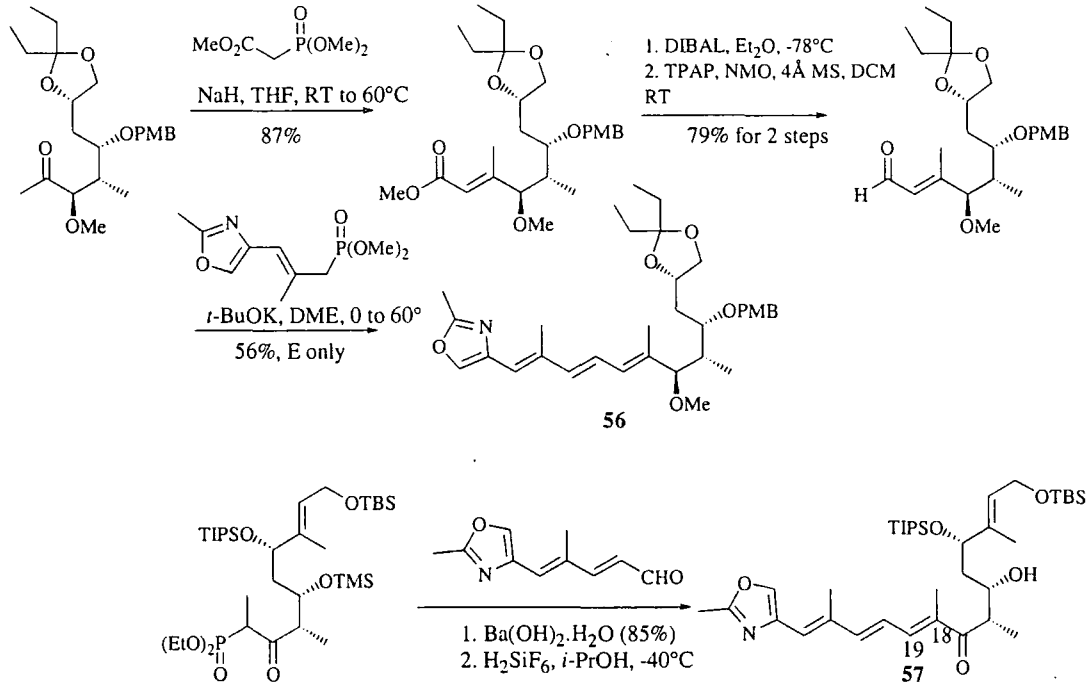
between aldehyde and triphenylphosphoranyl propanoate **50**, propanoate reduction, and oxidation to regenerate an aldehyde **51** (scheme 4).[38]

There are numerous applications of the HWE procedure towards polyene synthesis. A prominent example can be seen in Nicoloau's landmark total synthesis of amphotericin B **4**, in which three HWE reactions were used to construct the polyene section (scheme 5).[39]

The first two employed the functionalized phosphonate **53** leading to the acyclic hexaenal **54**, before the third reaction was used to induce ring closure, giving the cyclic heptaene **55**. A similar approach was taken by Mori's group in their recent synthesis of roxaticin **1**.[40]

The rhizoxins have attracted considerable attention owing to their remarkable biological activity,[21] and many efforts have been directed towards rhizoxin and its congeners.[41] Burke's partial synthesis of rhizoxin[41e] **14** (scheme 6) used two HWE reactions to form the trisubstituted *E*-olefin **56**.

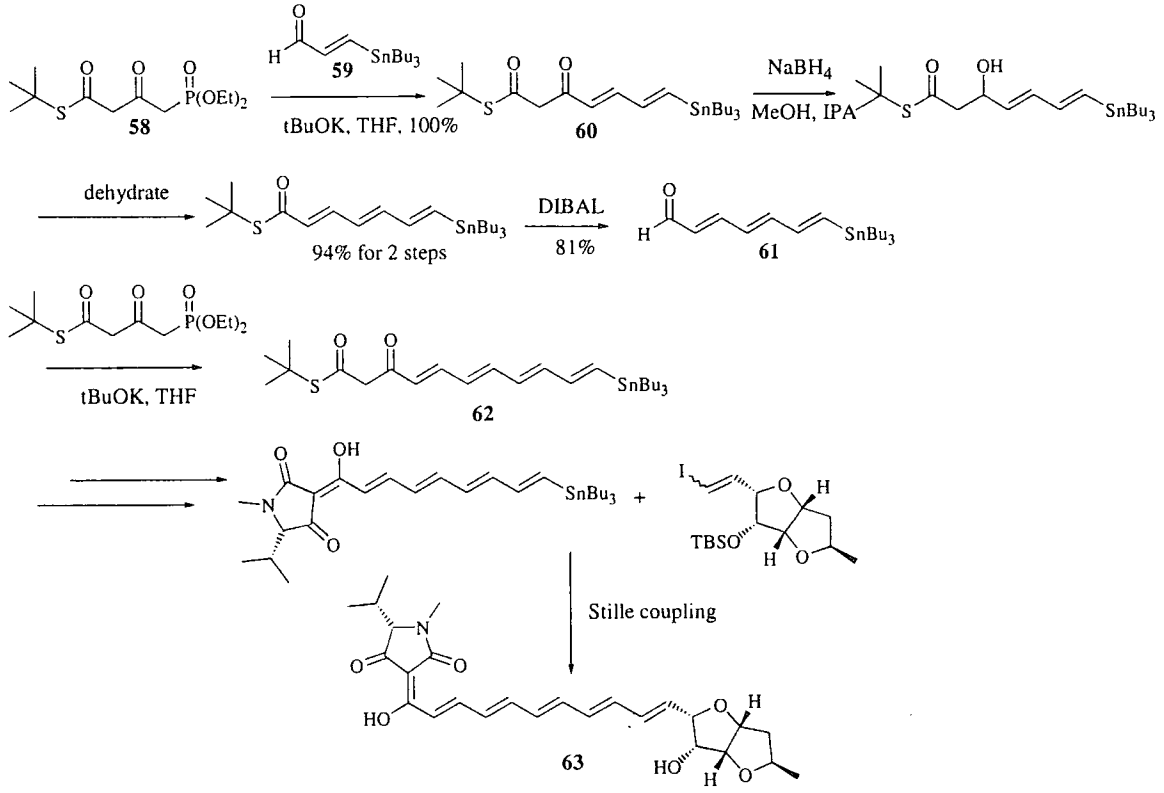
Scheme 6



Leahy's total synthesis of rhizoxin D utilizes a similar approach.[42] They explored various routes to the tricky triene oxazole fragment **57** before settling on a HWE reaction between C18 and C19. Ley's group used HWE reactions to install the acyltetramic acid portion of the antibiotic erythroskyrine **63** (scheme 7).[43,44] They coupled the phosphonate ester **58** with the β-tributylstannyl aldehyde **59** under optimized conditions, giving the dienyl stannane **60** quantitatively as a >30:1 mixture of *E*/*Z* isomers.

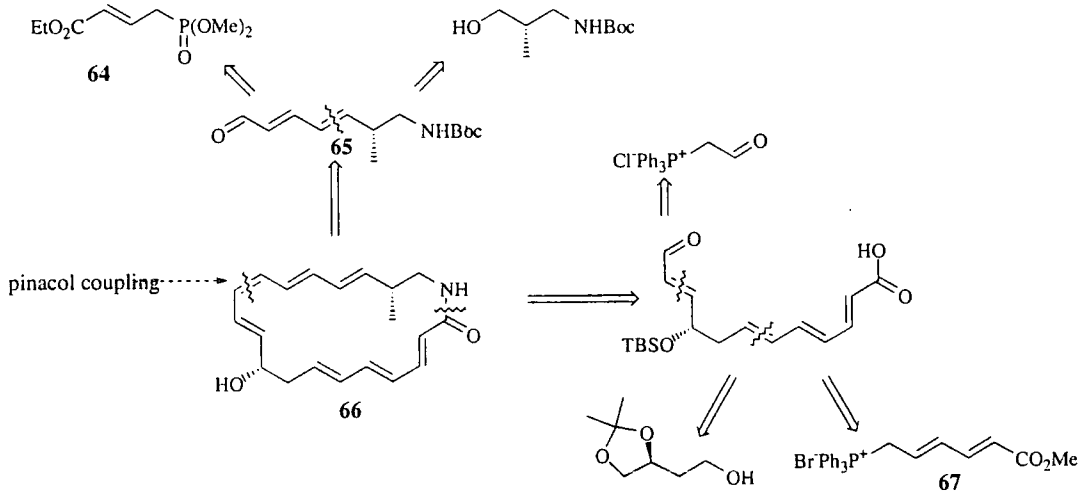
Subjection of trienal **61** and phosphonate **58** to HWE reaction under identical conditions provided the tetraene **62** with high yield and high selectivity (>30:1 *E*/*Z*).

Scheme 7



Phosphorous ylide based reactions played a pivotal role in the construction of the macrocyclic lactam cyclamenol A **66** (scheme 8), recently reported by Waldmann.[45]

Scheme 8

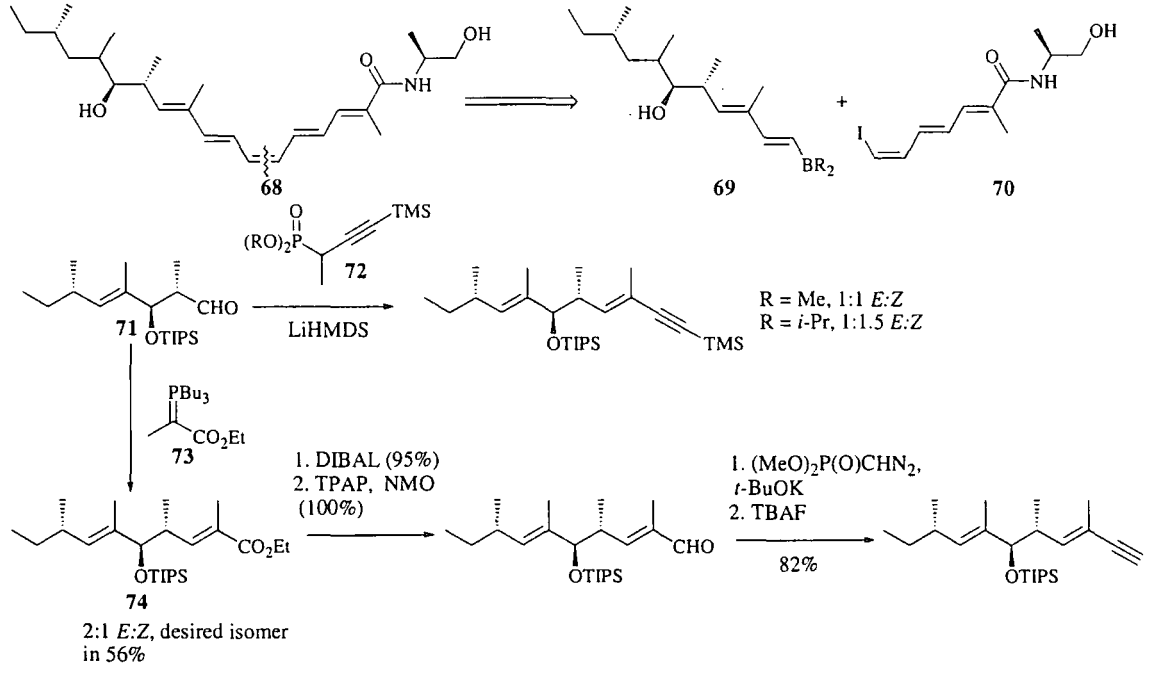


In devising their synthetic strategy, the authors paid particular attention to the polyene section, which comprised one *Z* and six *E* double bonds. It was feared that the *Z* double bond would isomerize, or the polyene skeleton would react further to give a fully conjugated octaene. For this reason, construction of the polyene system was left until

late in the synthesis, and the final *Z* double bond was introduced *via* a pinacol coupling, allowing both ends of the acyclic precursor to be tied together through template control. A HWE procedure involving crotonyl phosphonate **64** was used to construct the dienal **65**, whilst a Wittig reaction exploiting the phosphonium salt **67** derived from sorbic acid was used to provide the southern triene.

So far, only examples of the Wittig and HWE reactions leading to all *E* polyenes have been examined; this is mainly due to the inherent *E*-selectivity of these processes. It is possible however, either by changing the nature of the phosphonium salt/phosphonate or by varying the reaction conditions, to bias the outcome towards either alkene isomer. In the first reported synthesis of myxalamide A **68** (scheme 9), the most abundant of the four myxalamides[46] isolated from the gliding bacteria *Myxococcus xanthus,* Heathcock and co-workers opted to complete the synthesis *via* a Suzuki coupling (see **2.2**) between dienylboronic acid **69** and iodotriene **70**.[47]

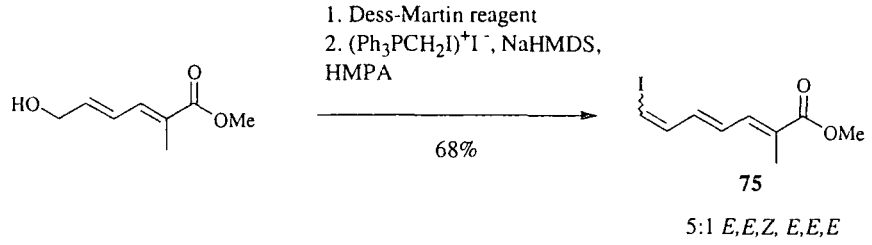
Scheme 9



In order to prepare the enyne precursor that would undergo hydroboration to give **69**, they initially attempted to install the triple bond *via* a HWE reaction between aldehyde **71** and phosphonate **72**. However, *E/Z* selectivities were not good, and use of the bulkier phosphonate gave greater selectivity, but in the wrong direction. Use of the stabilized ylide **73** gave the unsaturated ester **74** in an improved 2:1 (*E/Z*) ratio. Synthesis of the triene portion of iodotriene **70** (scheme 10) required formation of an (*E,E,Z*)-alkenyl unit **75**, with insertion of the *Z*-alkene being accomplished under kinetic conditions through the Stork-Zhao modification of the Wittig reaction.[48] Unfortunately,

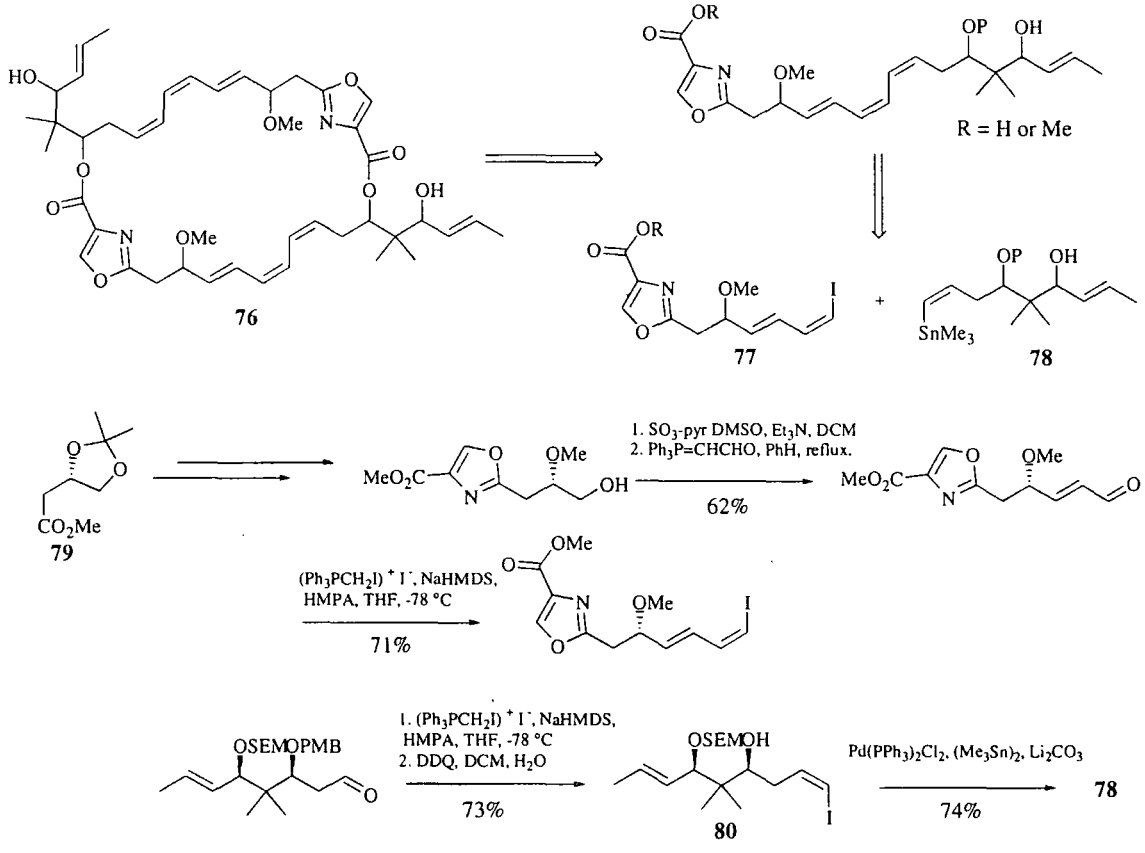
although the ratio of isomers was acceptable, separation by a variety of methods proved impossible, and the authors were forced to use an alternative approach to this fragment.

Scheme 10



This modification[48] was also employed in Meyer's synthesis of the monomeric unit of diorazole C_1 **76** (scheme 11).[49]

Scheme 51

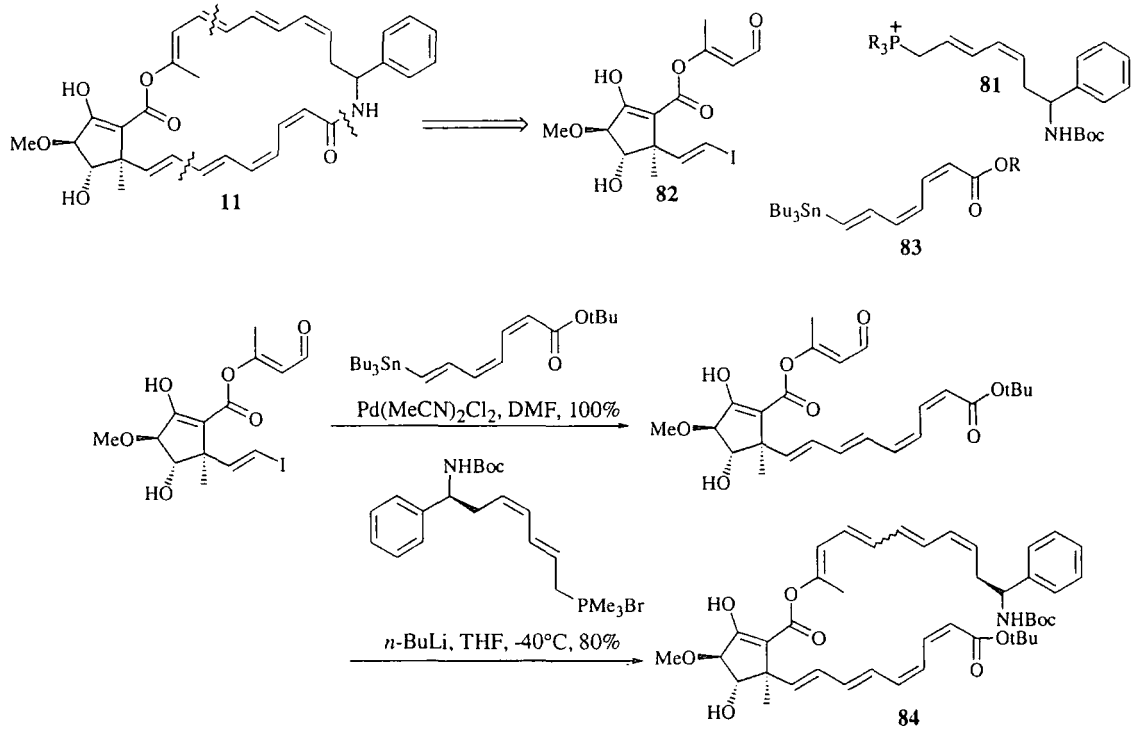


Here, a palladium coupling reaction was also chosen as the final bond-forming reaction, which retrosynthetically led back to an oxazole containing dienyl iodide **77** and a *cis*-alkenyl stannane **78**. Iodide **77** was assembled from readily available ester **79**, via Wittig homologation to insert the *trans* double bond, followed by the Stork-Zhao Wittig modification. This strategy was used again to furnish alkenyl iodide **80**, which gave **78** after the Stille coupling.

The same group also recently reported studies towards the total synthesis of viridenomycin[50] **11** (scheme 12), a large polyene macrolide containing two mixed

geometry tetraenes. In their second generation approach, the authors chose to disconnect **11** into three key fragments, allowing these two potentially problematic units to be synthesized in isolation.

Scheme 6



It was envisaged that **81** would be joined to the core cyclopentenol fragment **82** using phosphonate chemistry and **81** was prepared accordingly, with a kinetic Wittig reaction being used to insert the required *Z*-alkene with good selectivity. The original strategy to use a phosphonate to join **81** and **82** failed in studies using model aldehydes (entries 1 & 2, table **2**), as rearrangement to give a ketone was observed. Use of the semi-stabilized ylide described by Tamura[51] gave poor *E*/*Z* selectivity (entries 3 & 4). In the end, the authors used trimethylphosphonium salt **81** (R=Me) to prepare **84**, which gave high selectivity towards the desired *E* isomer. A kinetic HWE reaction was employed to synthesize the trienyl stannane **83** (scheme 13); use of the electrophilic Still-Gennari phosphonate[52] under kinetic conditions that favour rapid elimination leads to *Z*-alkenes in excellent isomeric purity. Unfortunately, removal of both *t*-Bu protecting groups proved impossible, and cyclization of **84** was not realized.

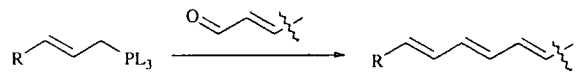
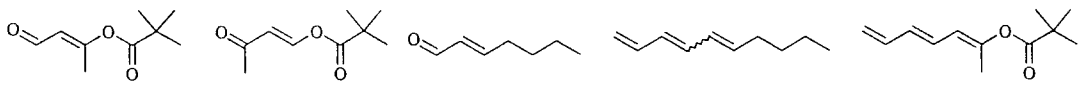


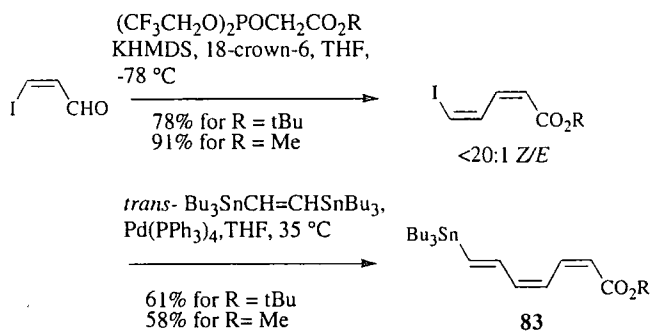
Table 2: *E/Z* selectivities in the HWE reaction between various ylids 81 and model aldehydes 85-87.

Entry	R	PL_3	Base	Aldehyde	Product	Ratio (E:Z)
1	Me	$PO(OEt)_2$	KO*t*-Bu	**85**	**86**	---
2	Me	$PO(OEt)_2$	*n*-BuLi	**85**	**86**	---
3	H	PBu_3	KO*t*-Bu	**87**	**88**	2.6 : 1
4	H	PBu_3	*n*-BuLi	**87**	**88**	2.9 : 1
5	H	PMe_3	KO*t*-Bu	**87**	**88**	3.0 : 1
6	H	PMe_3	*n*-BuLi	**87**	**88**	30 : 1
7	H	PMe_3	*n*-BuLi	**85**	**89**	10 :1 (90%)



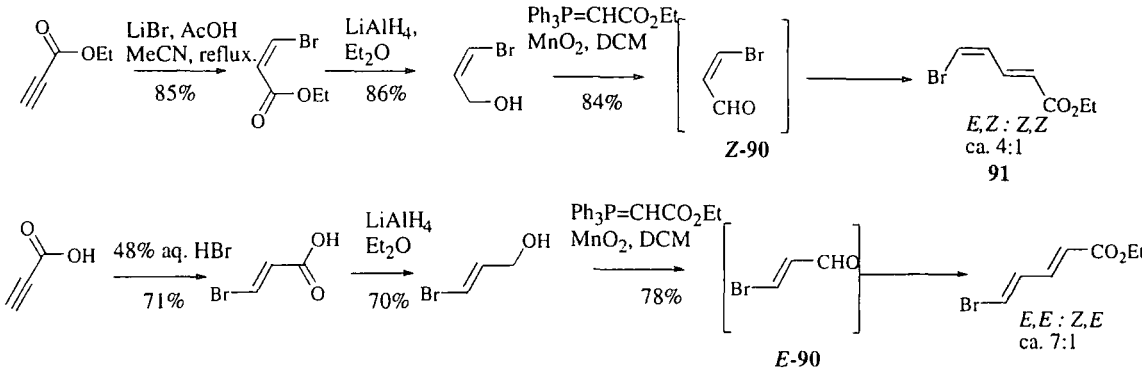
85 **86** **87** **88** **89**

Scheme 13



Taylor's group recently disclosed a procedure that enables elaboration of haloenals **90** without the need for their isolation.[53] This is useful because whilst such compounds are potentially valuable as polyene building blocks, they are also unstable, difficut to isolate, and have a severe irritant effect on mucous membranes, particularly the bromo and chloro-enals (both isomers of iodopropenal can be prepared readily, but retain lachrymatory properties). Their protocol involves *in situ* manganese dioxide haloenol oxidation, followed by direct Wittig homologation, giving dienyl haloesters **91** that are themselves useful polyene buildings blocks, given that partial reduction of the ester function would allow the process to be repeated (scheme 14).

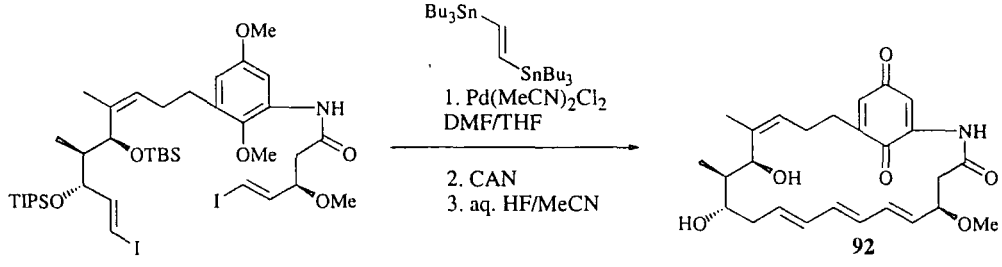
Scheme 14



1.8 Transition metal based strategies

Representative of these strategies are the palladium cross-coupling reactions, allowing single bond formation between two sp^2 centres with excellent stereoselectivity and often under very mild conditions, and without some of the problems encountered with more traditional approaches. The mildness and functional group tolerance of these reactions makes them an ideal way to insert the final 'stitch' in a polyene chain, thus allowing this often troublesome section to be assembled last. The Stille reaction[54] is particularly useful, and typically proceeds with retention of configuration of the alkenyl halide, leading to polyenes of exceptionally high geometrical purity. This reaction has been exploited many times, for example, in Nicolaou's synthesis of rapamycin **12**[55] and Panek's synthesis of mycotrienin I and mycotrienol **92**[56](scheme 15), and in the previously discussed syntheses of myxalamide A **68**, viridenomycin **11**, erythroskyrine **63**, and the monomeric moiety of disorazole C_1 **76**.

Scheme 15



Duchene and Parrain have successfully applied Stille methodology to a variety of retinoids, including the trifluoromethyl retinoate **96**,[57] useful as a biological probe (scheme 16). Their methodology uses enyne precursor **94** derived from β-ionone,[58] which may either be converted into dienylstannane **95a** by treatment with the Lipshutz reagent[59] in the presence of methanol, or into the trisubstituted vinylstannane **95b** by trapping the intermediate vinylcuprate with methyl iodide. Stille couplings of β-iodovinylic acids **98** derived from tetrolic acid via iodides **97**, with stannanes **95** gives the retinoids stereoselectively (table 3).[60] Fluorine substituted polyenes have

traditionally been obtained *via* HWE or Julia reactions, but these methods are hampered by poor *E/Z* selectivity, particularly when forming the 9-*trans* trisubstituted double bond common in many retinoids. Yosihara has recently described a preparation of 9-*trans*-9-desmethyl-9-fluororetinal **101** and analogues based upon a four component coupling approach.[61] Due to the failure of the 4-hydroxybutynoate **100** to undergo fluorination under reported conditions, the second approach utilizing Wittig, HWE and Stille chemistry was successfully adopted (scheme 17).

Scheme 16

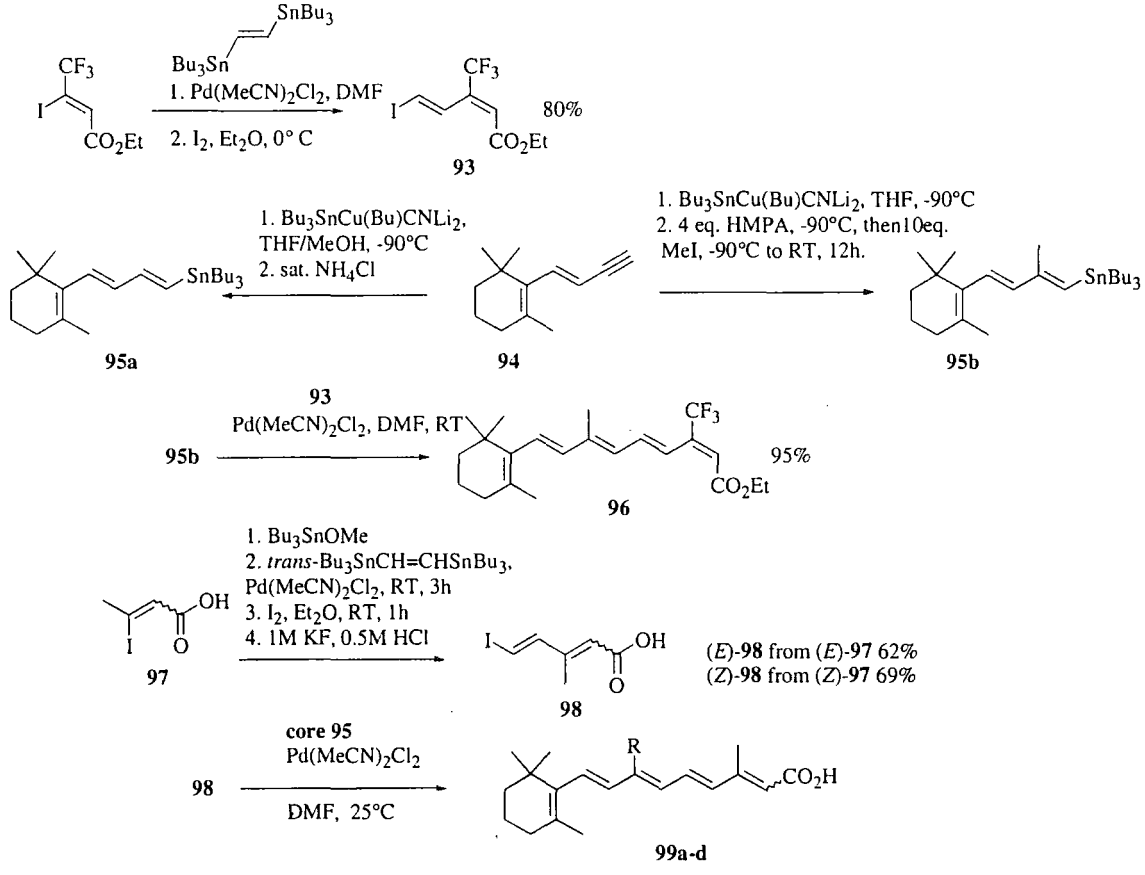
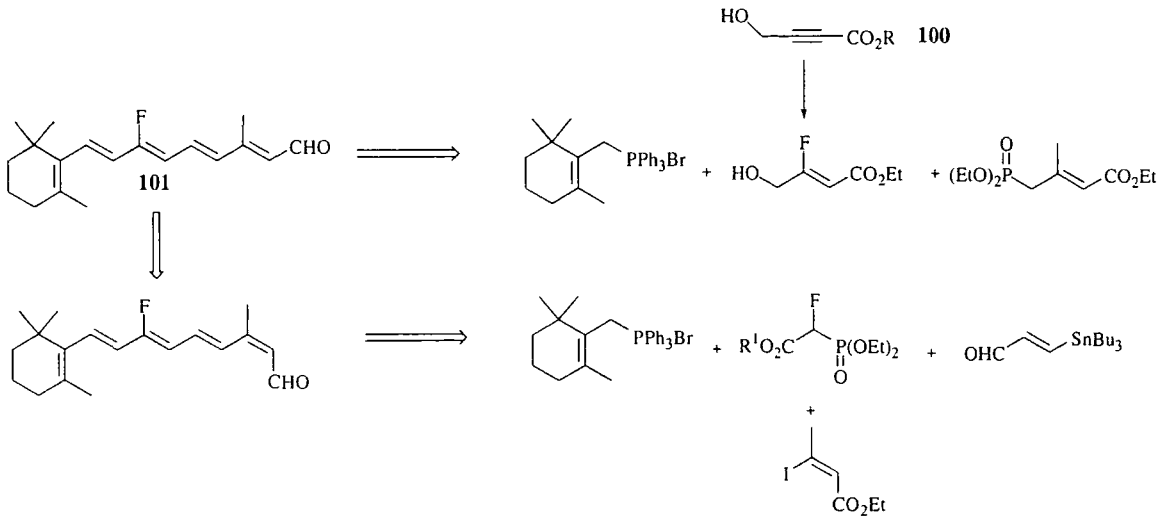


Table 3: Stille couplings between cores 95 and iodides 98 to access a variety of mixed geometry retinoic acids

core	iodide	retinoic acid	yield (%)
95a	(*E*)-**98**	all *trans*-9-nor-retinoic acid	50
95a	(*Z*)-**98**	(13Z)-9-nor-retinoic acid	45
95b	(*E*)-**98**	all-*trans* retinoic acid	73
95b	(*Z*)-**98**	(13Z)-retinoic acid	70

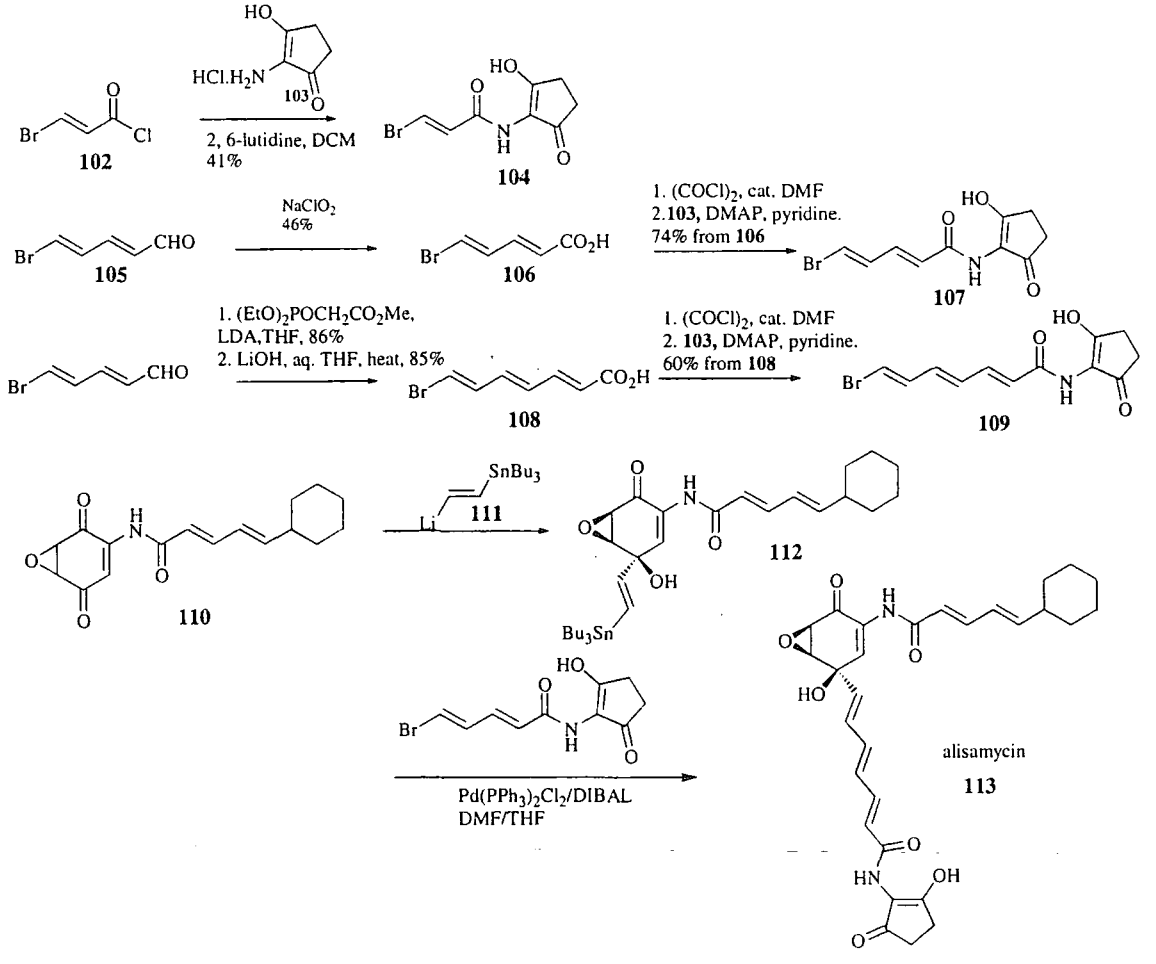
[a] see fig 7 for retinoid numbering.

Scheme 17



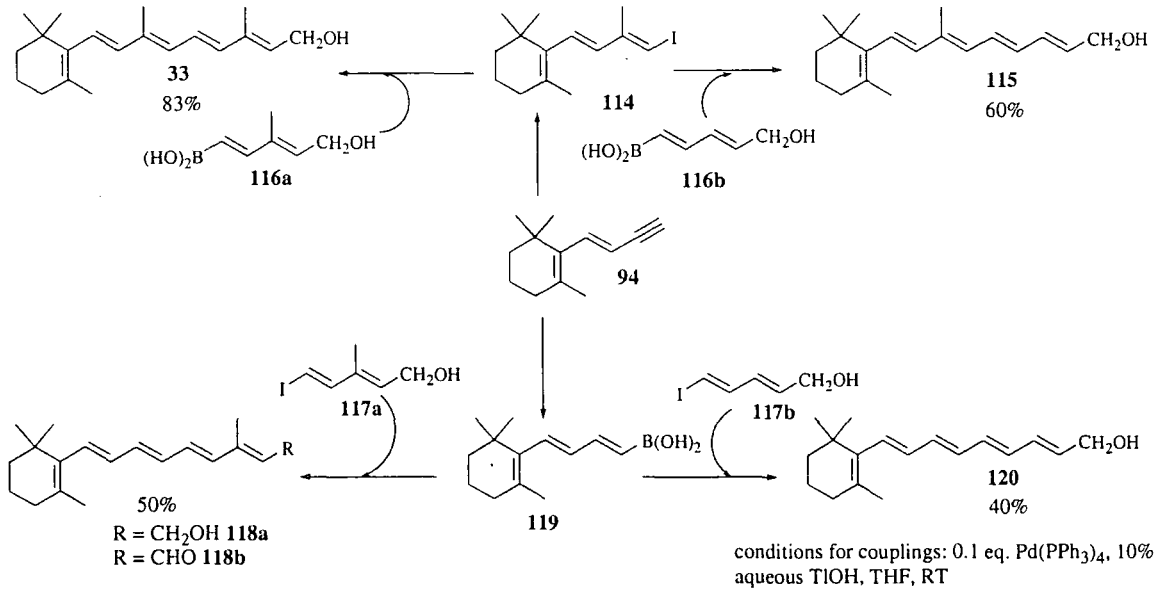
De Lera and co-workers have also exhaustively examined applications of the Stille reaction for the synthesis of retinoid skeletons. They studied various disconnections and then developed optimized approaches for each strategy, providing useful information regarding the influence of steric factors on the Stille reaction, as well as useful retinoid building blocks.[62]

Scheme 18



The first complete synthesis of a manumycin antibiotic was achieved by Taylor with alisamycin **113** (scheme 18).[63] Fundamental to this synthesis was the introduction of the unsaturated 2-amino-3-hydroxycyclopentenone forming the lower polyene chain. This moiety is present in many *Streptomyces sp.* metabolites, notably in many of the manumycin antibiotics. Taylor chose to insert this portion *via* Stille reaction of 2-amino-3-hydroxycyclopentenone halides and vinylstannanes, thus treatment of known acyl chloride **102** with key amine hydrochloride **103** (prepared from cyclopentanedione) leads to vinyl bromide **104**. Higher vinylogues **107** and **109**, suitable for synthesizing the manumycins, can be prepared *via* HWE homologation of bromodienal **105**. Elaboration of the quinone **110** with the Corey-Wollenberg reagent[64] **111** gave a mixture of enantiomeric vinylstannanes; Stille coupling of these with bromodiene **109** led to alismaycin and *ent*-alisamycin. Taylor's group have successfully applied this strategy to a great number of the manumycin antibiotics and related polyene natural products.[65]

Scheme 19

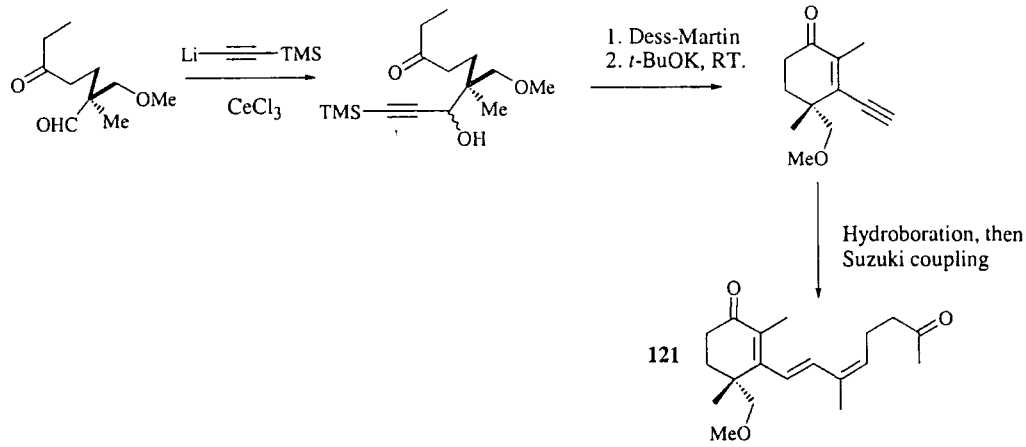


Like the Stille coupling reaction, the closely related Suzuki reaction[66] has found utility in polyene synthesis. Earlier work towards polyene synthesis was carried out by Suzuki, who successfully applied the reaction to the stereoselective synthesis of triene-containing natural products,[67] and later to the synthesis of trisporol B.[68] The Suzuki reaction can operate under extremely mild conditions making it an ideal way to synthesize potentially unstable polyenes. An example of this has already been seen in the total synthesis of myxalamide A, in which the synthesis was completed *via* Suzuki

coupling of **69** and **70**.[47] De Lera's group have also presented a detailed study of highly stereoselective retinoid syntheses achieved *via* the thallium-accelerated Suzuki reaction carried out under ambient temperatures. These mild conditions were chosen to be compatible with the known instability of vitamin A and its derivatives. Their approach illustrates the great flexibility offered by the palladium coupling reactions, in that the choice of which moiety to derive from the alkenyliodide or alkenylboronic acid is dictated by relative ease of preparation. Preparation of retinol and its 9- and/or 11-desmethyl analogues (scheme 19) was achieved through coupling of either boronic acids **116** with iodide **114** (also derived from enyne **94**), or with boronic acid **119** and iodides **117**, with total retention of the geometries of the coupling partners. The group have also used Suzuki chemistry for the stereocontrolled preparation of 9-desmethylretinoids, useful for bio-organic studies into protein-chromophore steric interactions involved in bacteriorhodopsin photocycles,[69] and more recently have applied Suzuki chemistry to the synthesis of 7-*cis*-retinoids.[70]

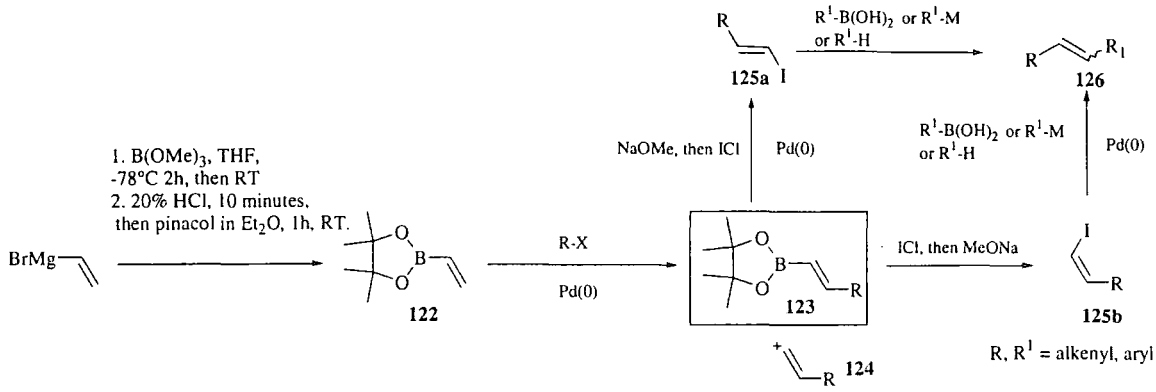
Several groups have been involved in applying Suzuki coupling methodology to leukotriene synthesis, including Sato's method for the preparation of LTB_3 and LTB_4.[71] Using similar conditions, Nicolaou has described the synthesis of a range of leukotriene A_4 derivatives.[72] Meyers and co-workers have been involved in the preparation of trisporic acids, a class of C_{18} isoprenoidal fungal hormones, utilizing Suzuki chemistry late-on to access the trisporol system (scheme 20).[73]

Scheme 20



Recently, Hénaff and Whiting reported a highly stereoselective approach to racemic phthoxazolin A **133** using a combination of palladium coupling reactions.[74] Their approach employs the vinylboronate **122** as a useful two-carbon building block for the synthesis of polyenes (scheme 21).[75]

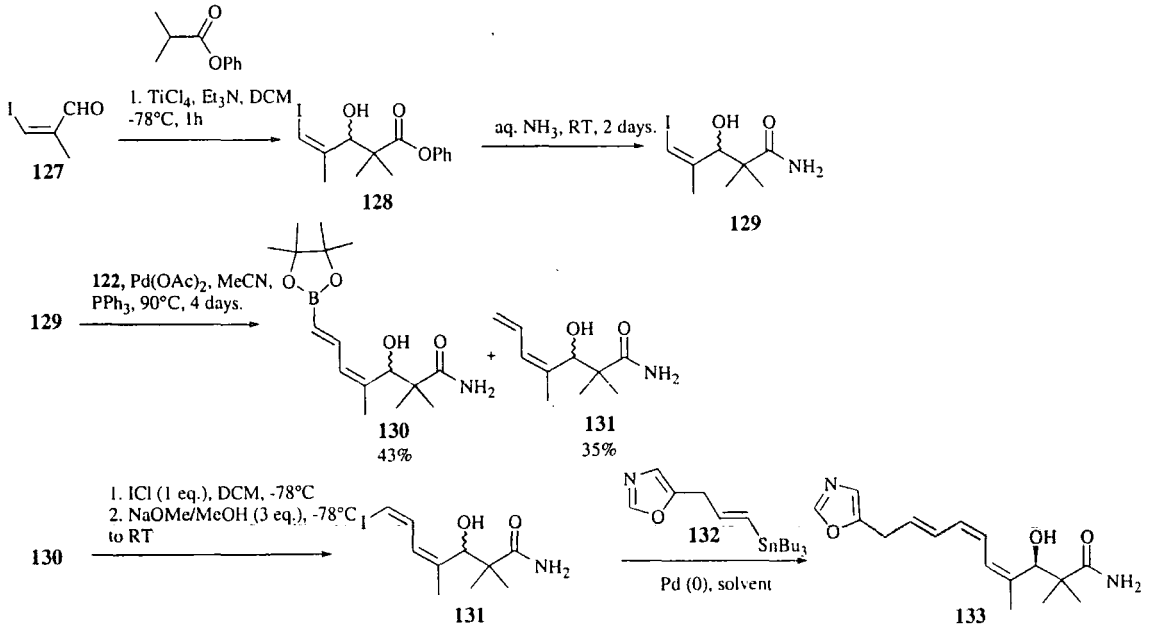
Scheme 21



Thus, coupling of **122** with suitable halides leads potentially to Heck or Suzuki products **123** and **124**, the ratio of which is dictated by many factors, including catalyst, solvent, temperature and the presence of additives.

Brown showed that vinylboronic acids could provide a stereocontrolled route to vinyl iodides, using iodide and sodium hydroxide to effect iodo-deboronation.[76] (and see **2.4.1.3**). The stereochemical course of the process is dictated by the order of addition of the reagents. Pinacol esters were found to be resistant to these conditions, requiring the use of ICl and sodium methoxide.[77] This provides access to vinyl iodides **125**, which may undergo coupling with alkenes or alkenyl metals, leading to dienes **126**. Subsequently, coupling of **126** with **122** leads to trienes if the iodo-deboronation procedure is repeated. Overall, **122** can be considered a vinyl dianion equivalent allowing rapid construction of stereodefined polyene systems. Application of this methodology to the herbicidal agent phthoxazolin A is outlined in scheme 22.

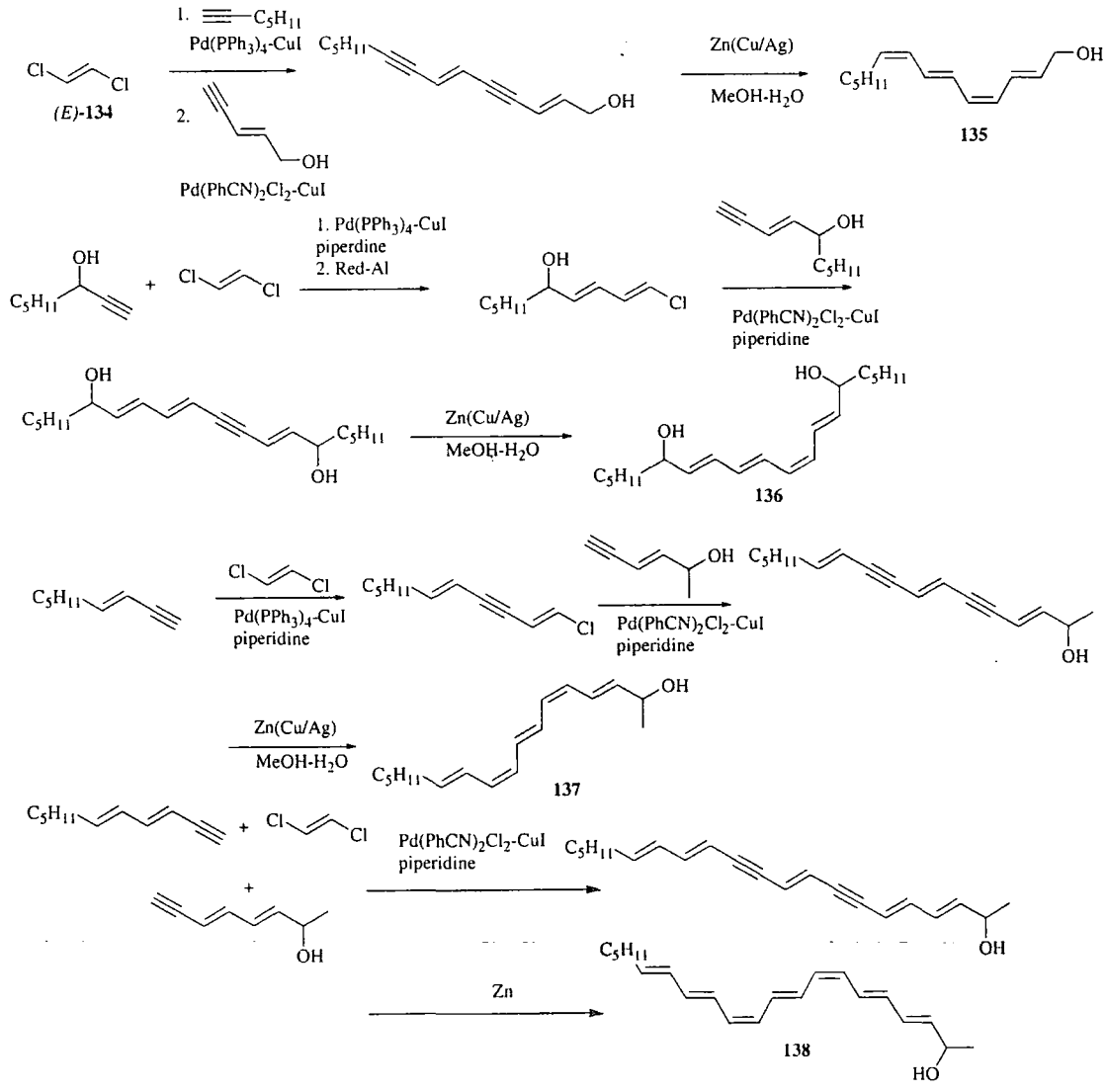
Scheme 22



Here, coupling of **122** and amide **129** (prepared from iodide **127** via an aldol reaction) demonstrates the functional group tolerance of these reactions, and gave the desired Heck product as the major product. Apart from this notable example, the Heck reaction, in its conventional guise, has found little utility in polyene synthesis. This is partially for the reason that, whilst the Stille reaction usually occurs with retention of stereochemical integrity of the coupling partners, the same cannot be said of the Heck reaction. Pattenden recently compared the Heck and Stille reactions in his synthesis of pateamine A, a macrolide containing a (*Z, E*)-diene acrylate moiety in its macrocylic core, and found the Stille reaction superior for this very reason.[78]

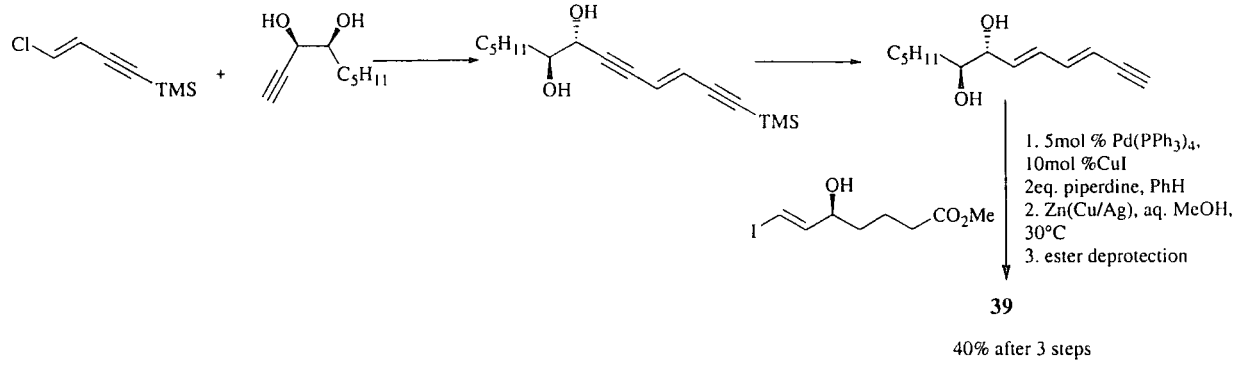
In contrast, applications of the alkyne coupling variant of the Heck reaction towards polyene synthesis, the so-called Sonagashira coupling,[79] are numerous. Alami's group have devised techniques for the stereocontrolled synthesis of polyenes by sequential coupling of 1,2-dichloroethylenes **134** with a variety of acetylenes; selective reduction of the acetylene then leads to geometrically pure polyenes **135-138** (scheme 23).[80]

Scheme 23



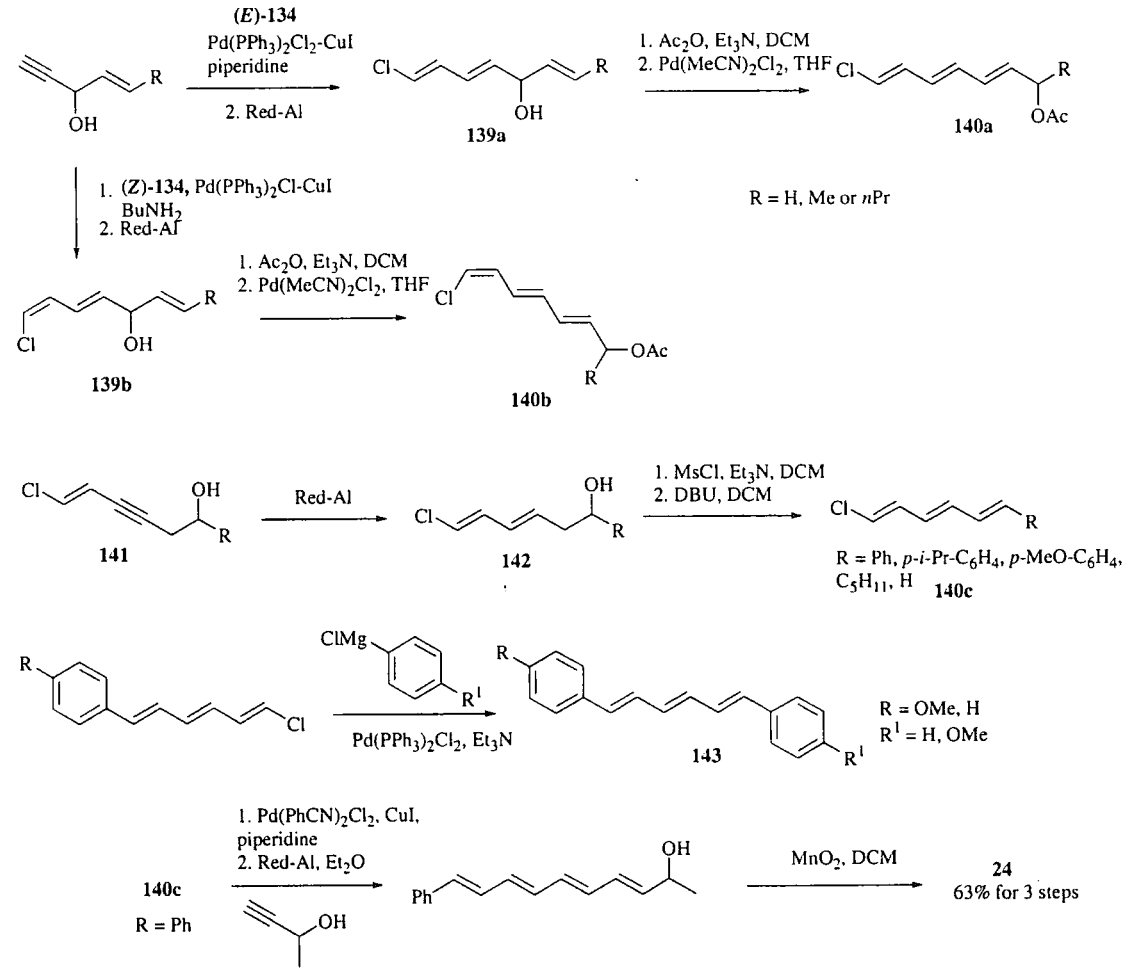
This methodology was applied to a short synthesis of lipoxin B **39** (scheme 24).

Scheme 24



The same group have also developed a related protocol for accessing all-*E* polyenes. This protocol is based around α-chloro-ω-substituted hexatrienes **140**, obtained by two different approaches (scheme 25).

Scheme 25

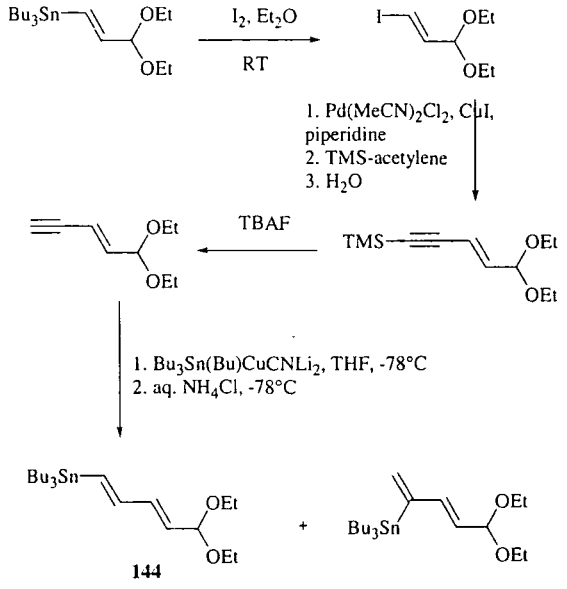


The first uses palladium catalyzed rearrangement of bis-allylic acetates, formed via bis-allylic alcohols **139**, whilst the second is based on the stereoselective reduction of homopropargylic alcohols **149** into (*E*)-homoallylic alcohols **142**, followed by elimination. Alcohols such as **142** may also be oxidized to give trienones and trieneals,

providing useful polyene building blocks having two reactive terminal functions, as the chlorine atom is able to participate in coupling reactions, with, for example, Grignard reagents, providing isomerically pure (*E,E,E*)-diaryl hexatrienes **143**. The coupling partner may be acetylenic, as illustrated in a brief, high-yielding synthesis of navanone B **24**.[81]

An obvious necessity for the palladium coupling reactions, when stereodefined polyenes are desired, is a feedstock of geometrically pure alkenyl halide or alkenyl metal. Many techniques giving access to these coupling partners have already been mentioned in this review.

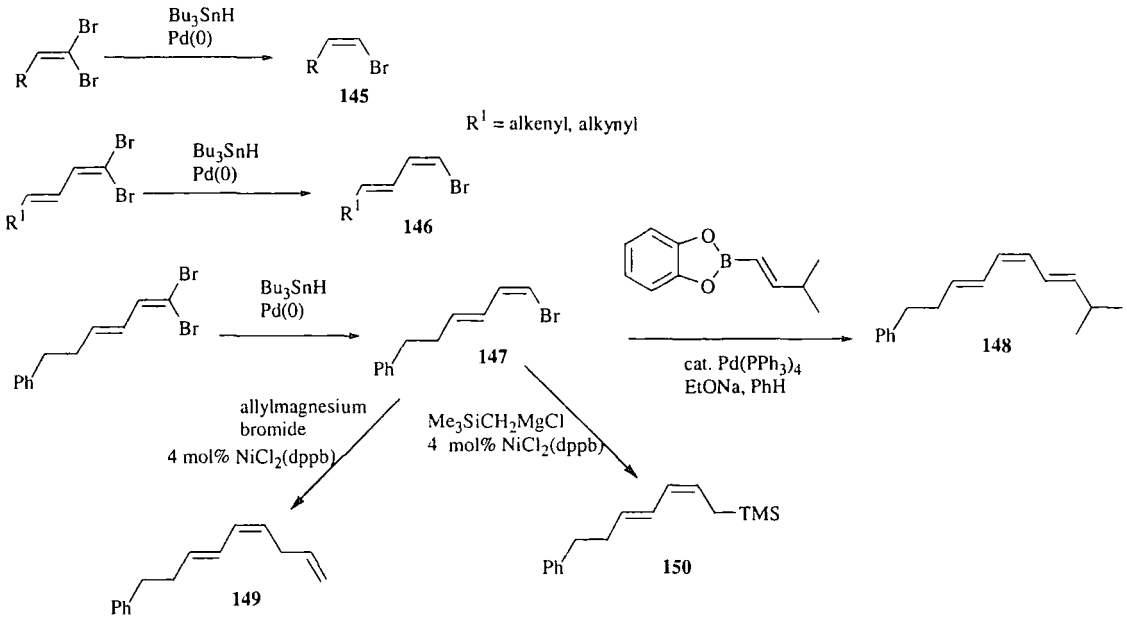
Scheme 26



Quintard has done work on the regioselectivity of organotin cross-couplings, tuning the reaction conditions in order to obtain the requisite (*E,E*) dienyltin acetals **144** that may then be used to construct polyenic systems (scheme 26).[82]

Uenishi's group have examined the stereoselective hydrogenolysis of 1,1-dibromoalkenes, providing access to (*Z*)-1-bromo-alkenes **145** that are useful for (*E,Z*)-diene synthesis.[83] Reduction of conjugated 1,1-dibromoalkenes affords 2-alkenyl or 2-alkynyl-substituted (*Z*)-1-bromo-1-alkenes **146**, useful synthons for polyene construction (scheme 27).

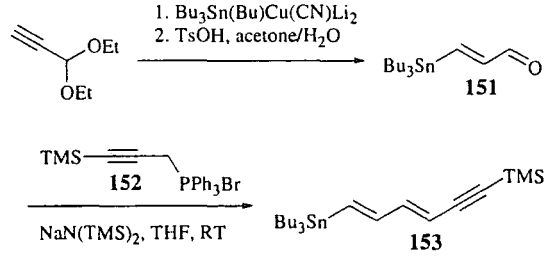
Scheme 27



These may then undergo coupling with boronic acids, giving stereodefined trienes such as **148**; coupling with alkynes is also possible. The validity of this approach to polyene synthesis was demonstrated by the synthesis of the unstable polyenes (11*Z*)-retinal and (2*Z*, 4*E*, 6*E*)-dehydrodendrolasin. The same group has also reported the nickel catalysed coupling of bromoalkenes **147** with Grignard reagents, giving potentially useful allylsilanes **150** when TMS-substituted Grignard reagents are employed, or alkylated 1,3-dienes e.g. **149** (scheme 27).[84]

Lipshutz has reported two highly specialized building blocks for the preparation of polyene systems. The first, stannylated dienyne **153**, is readily prepared through reaction of enal **151** with known Wittig salt **152** (scheme 28).

Scheme 28



Dienyne **153** undergoes cross-coupling at the vinylstannane end with a variety of halides under different conditions, producing trienyne or tetraenyne products (table 4).[85] Elaboration of the alkyne terminus of these products may be carried out either through initial hydrozirconation, transmetallation with aluminium, and trapping of the alane with a suitable electrophile, or via direct Negishi carboalumination followed by

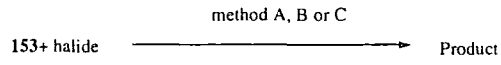
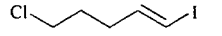
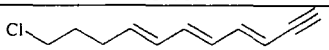
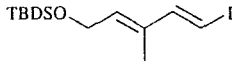
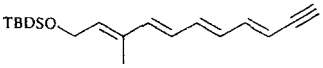
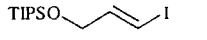
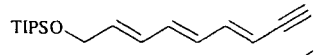
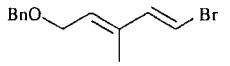
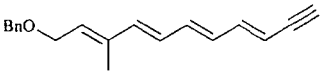
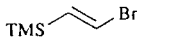
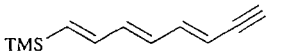
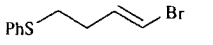
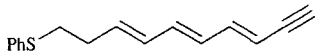


Table 4: Different methods for the coupling of alkenyl halides with lynchpin 153 to yield polyenynes.

Halide	Method	Product	Yield (%)
	A		83
	A		74
	A		80
	A		82
	B		72
	C		91

[a] method A: i). BuLi, THF, -78°C; ii). $ZnCl_2$, 0°C; iii) $Pd(PPh_3)_4$; iv) K_2CO_3, EtOH. method B: i)1.5eq. CuCN, $Pd_2(dba)_3$, $AsPh_3$, NMP, 50°C; ii)K_2CO_3, EtOH. method C: i)1.5eq. CuCN, $Pd_2(dba)_3$, $P(Fur)_3$, NMP, 50°C; ii)K_2CO_3, EtOH.

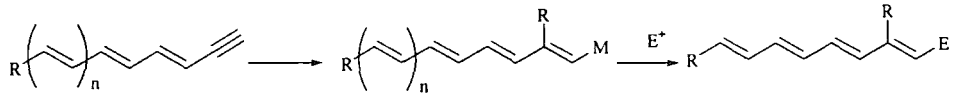
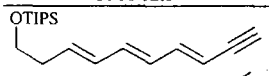
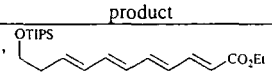
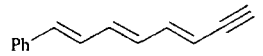
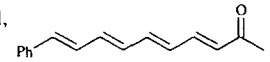
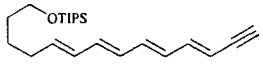
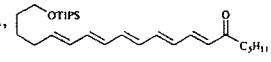
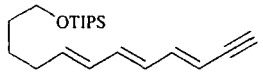
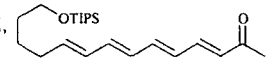
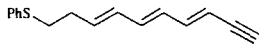
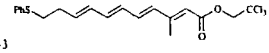


Table 5: Elaboration of acetylenic substrates to yield polyenic products

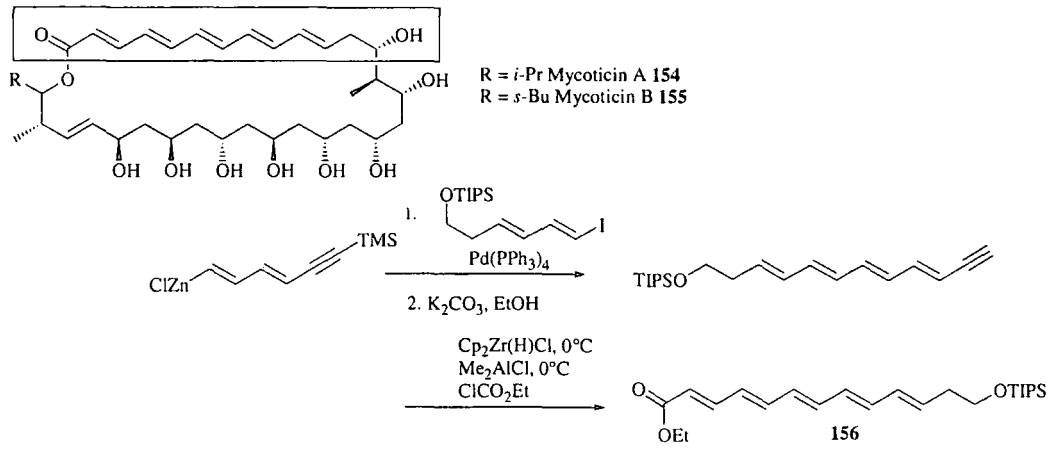
Substrate	Yield (%)	metallation / electrophile	product	Yield (%)
	70-A	$Cp_2Zr(H)Cl$, DCM, Me_2AlCl, 0°C, $ClCO_2Et$		71
	73-A	$Cp_2Zr(H)Cl$, DCM, Me_2AlCl, 0°C, ClCOMe		82
	74-A	$Cp_2Zr(H)Cl$, DCM, Me_2AlCl, 0°C, C5H11COCl		80
	75-A	$Cp_2Zr(H)Cl$, DCM, Me_2AlCl, 0°C, ClCOMe		83
	91-B	Me_3Al, $Cp_2Zr(H)Cl$, $ClCH_2CH_2Cl$, $ClCO_2CH_2CCl_3$		73

[a] prepared from **153** and the corresponding vinyl halide by methods A or B, *cf.* table **4**

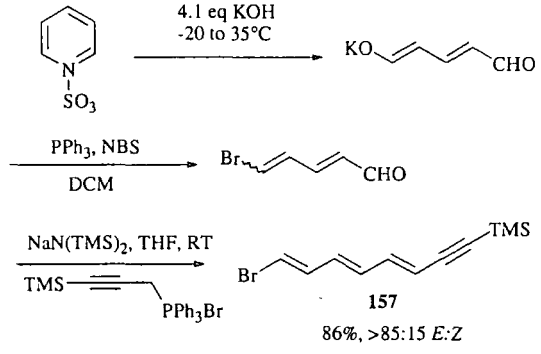
quenching. Both processes give rapid access to a variety of all-*E* polyenes (table 5). A synthesis of navenone B **24** is a noteworthy example.

The method has further applications to natural products, for instance, preparation of the oxopentaene **156** common to the mycoticins **154-155** (scheme 29).

Scheme 29



Scheme 30



Access to vinylogs of retinoic acid is also possible. Their redesigned trienyne (scheme 30) **157** incorporates an inversion of polarity relative to **153** due to replacement of the stannyl diene moiety by vinylic bromide. **157** can thus undergo coupling with vinyl and dienylzinc reagents (table 6). Elaboration of the alkyne terminus in the usual manner, either prior to, or after an initial coupling at the vinyl bromide terminus, leads to oxopolyenes, and this approach was applied to a short synthesis of the oxohexaene **159**, common to the dermostatins, of which dermostatin A **160** may be taken as a typical member (scheme 31).[86]

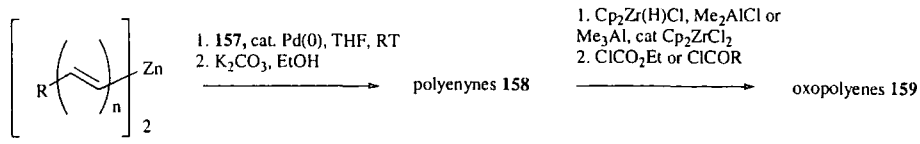
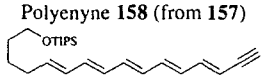
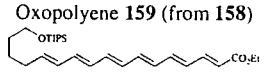
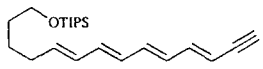
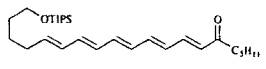
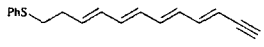
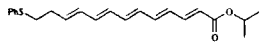
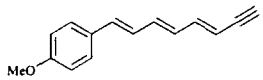
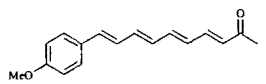
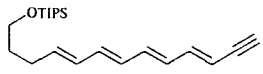
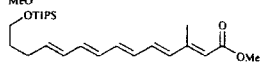
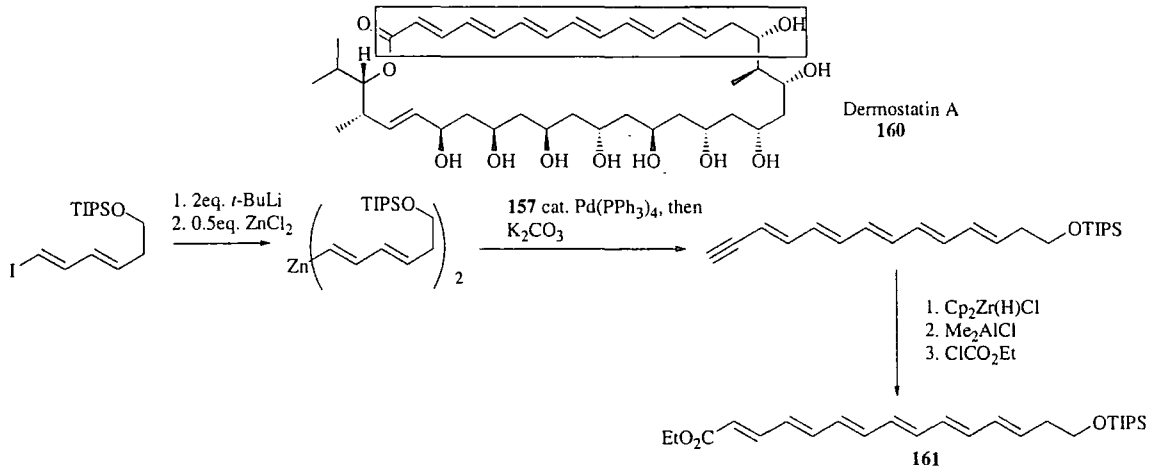


Table 6: Functionalization of polyenynes to yield oxopolyenes

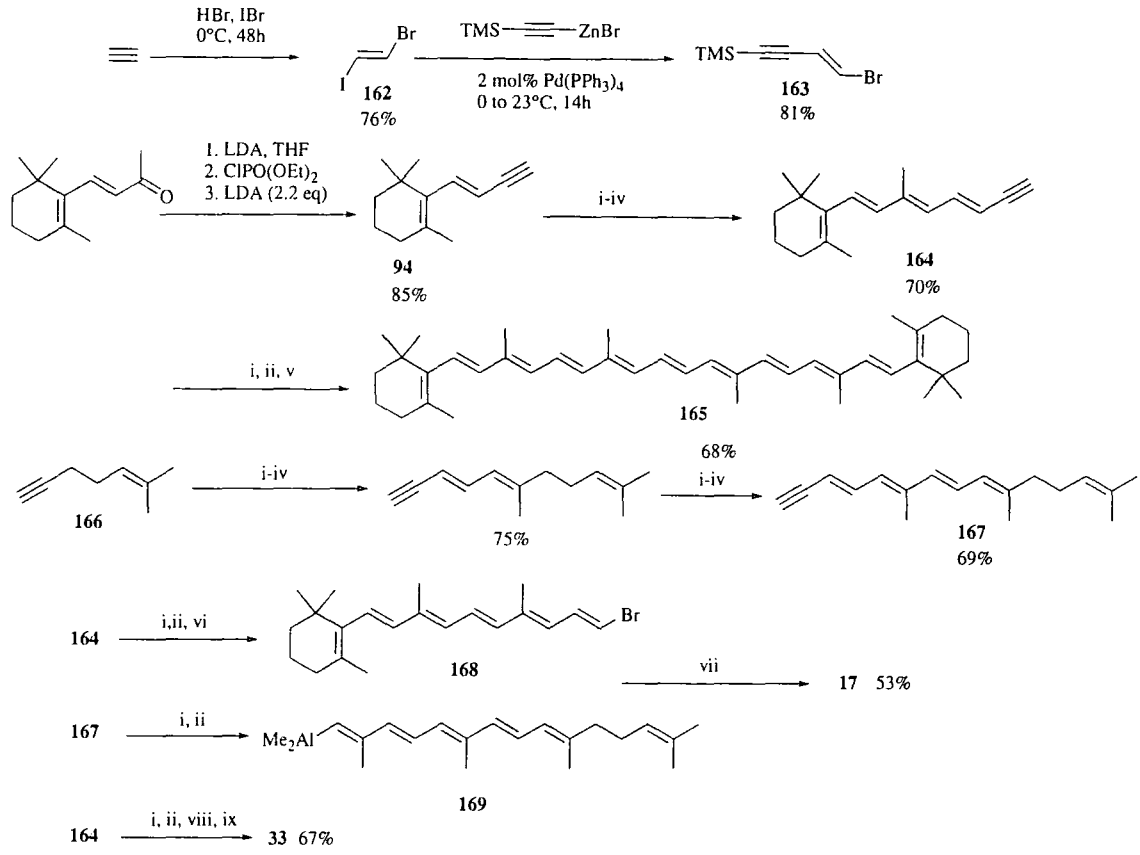
Polyenyne **158** (from **157**)	Yield (%)	Metalation/Electrophile	Oxopolyene **159** (from **158**)	Yield (%)
	78	$Cp_2Zr(H)Cl$ Me_2AlCl $ClCO_2Et$		68
	73	$Cp_2Zr(H)Cl$ Me_2AlCl $ClCO_2Et$		73
	80	cat. Cp_2Zr_2Cl Me_3Al $ClCO_2$-*i*-Bu		75
	85	$Cp_2Zr(H)Cl$ Me_2AlCl ClCOMe		70
	73	cat. Cp_2ZrCl_2 Me_3Al $ClCO_2Me$		74

Scheme 31



Negishi has formulated a highly efficient and stereoselective procedure for the preparation of both symmetrical and unsymmetrical carotenoids. This procedure is based upon Zr-catalyzed carboalumination of conjugated oligoenynes followed by palladium and zinc catalyzed cross-coupling of the resultant alkenylalanes and allows ready access to members of the retinoids family. The procedure utilitizes the two and four carbon synthons **162** and **163** respectively. Accordingly, dihaloalkene **162** is readily converted to **163**; with these in hand the authors were able to prepare a variety of carotenoids *e.g.* β-carotene **165** was prepared in 41% overall yield in three linear steps from **94**. In a similar fashion γ-carotene **17** and vitamin A **33** were prepared in good yields (scheme 32). It is noteworthy that in all cases, ≥99% stereoselectivity towards the drawn isomer was observed, leading to ≥ 99% isomerically pure polyenes.[87]

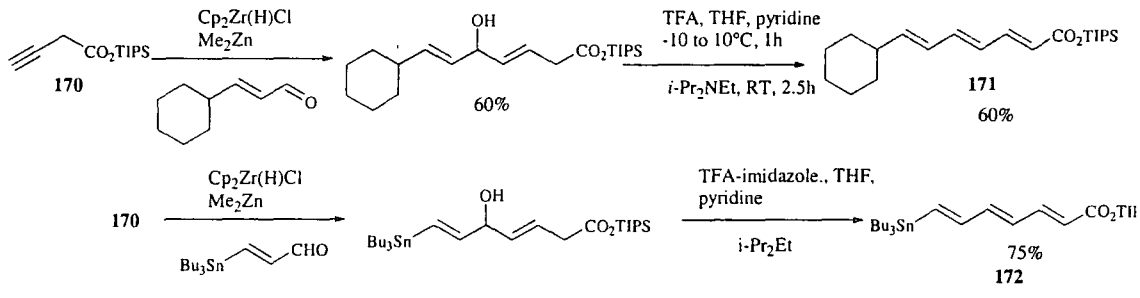
Scheme 32



Conditions:
i. Me_3Al (2eq.), Cp_2ZrCl_2 (1eq.), $(CH_2Cl)_2$, 23°C, 4h; ii. evaporation at 50°C and <0.5mmHg; iii. **163** (1.05eq.), $ZnCl_2$ (1eq.) in THF, 2.5mol % $Pd_2(dba)_3$, 10mol % $P(Fur)_3$, DMF, 23°C, 6h; iv. K_2CO_3, MeOH, 23°C, 3h; v. **162** (0.5eq), $ZnCl_2$ (1eq.) in THF, 2.5mol % $Pd_2(dba)_3$, 10mol % $P(Fur)_3$, DMF, 23°C, 8h; vi. **162** (1.05eq), $ZnBr_2$ (1eq.) in THF, 5mol % $Pd(PPh_3)_4$, DMF, 23°C, 2h; vii. $ZnCl_2$ (1eq.) in THF, 2.5mol % $Pd_2(dba)_3$, 10mol % $P(Fur)_3$, DMF, 23°C, 6h; viii. THF, *n*-BuLi (1eq.), 23°C, 0.5h; ix. $(CH2O)_n$, 23°C, 5h.

Wipf's group have prepared members of the manumycin family, using organozirconocene methodology to build the polyene sections.[88]

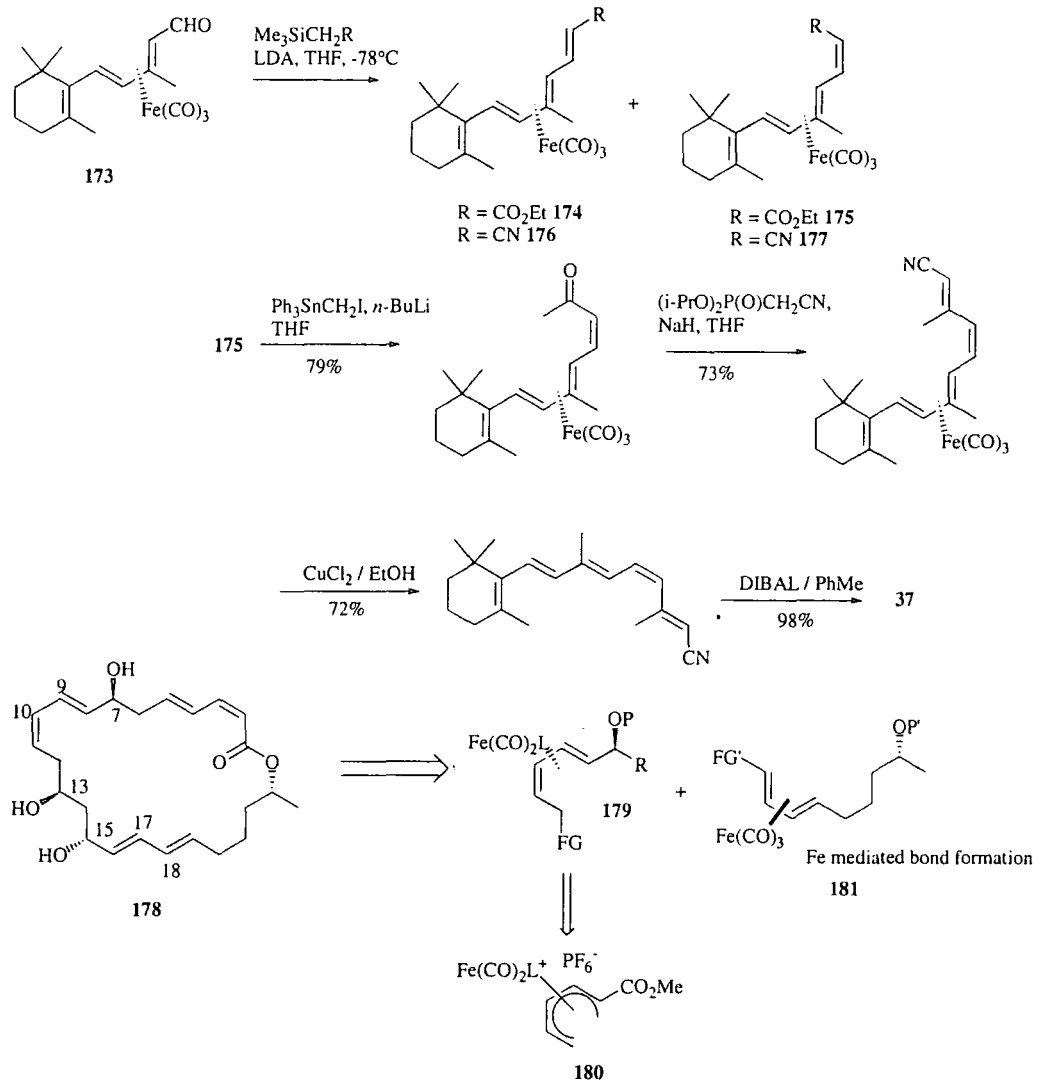
Scheme 33



This approach involves hydrozirconation of a functionalized alkyne *e.g.* **170**, followed by transmetalation with zinc, and *in situ* 1,2-addition of the organozinc reagent to α,β-unsaturated aldehydes. The approach is convergent and can be used to synthesize dienyl and trienyl side chains common to the manumycins, and facilitates analogue preparation. Scheme 33 exemplifies this protocol through the synthesis of the eastern side chain of asukamycin **171** and southern side-chain of nisamycin **172**.

Two recent applications of organoiron methodology towards polyene synthesis have been disclosed (scheme 34).

Scheme 34

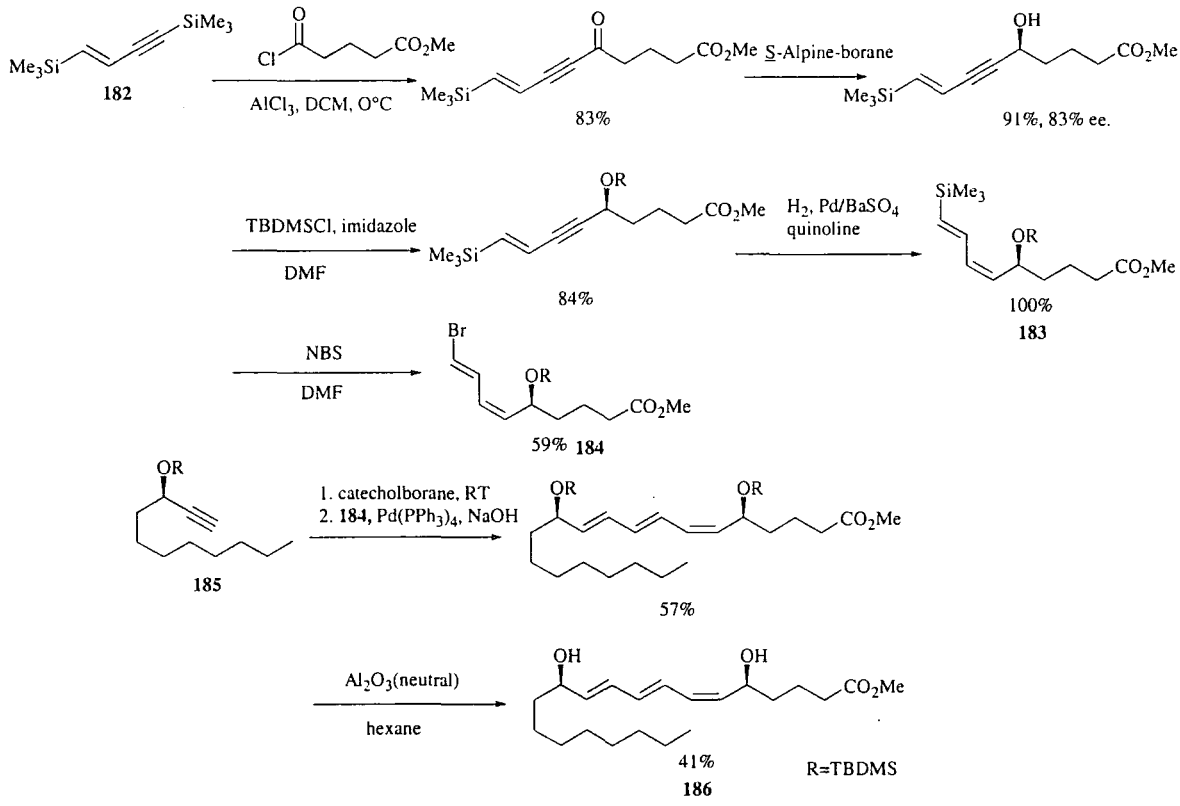


The first, aimed at stereoselective retinoid synthesis, uses a Peterson reaction between β-ionylideneacetaldehyde-tricarbonyliron complex **173** and a range of trimethylsilyl derivatives to access retinoid precursors **174-177**. Iron complex **175** was subsequently transformed into 11*Z*-retinal **37** by conventional means.[89] The second application employs stoichiometric acyclic dienyl iron complexes. Accordlingly, macrolactin A **178** was disconnected into fragments **179** and **181**, with a view to joining them together via nitrile oxide-olefin cycloaddition methodology. The (*E*, *Z*)-diene segment of **179** was prepared through addition of the strongly nucleophilic lithium anion of 2-(trimethylsilyl)ethyl nitroacetate to the isolable *cisoid* cation **180**, giving an initial mixture of diastereomers that rearranges completely to the (*E*, *Z*) complex upon standing in chloroform.[90]

1.9 Miscellaneous methods

Several new methodologies have emerged recently for the preparation of polyenes. Naso and co-workers have successfully used bis(trimethylsilyl) derivatives to construct a variety of natural products, including the potent leukotriene B_3 methyl ester **186** (scheme 35).

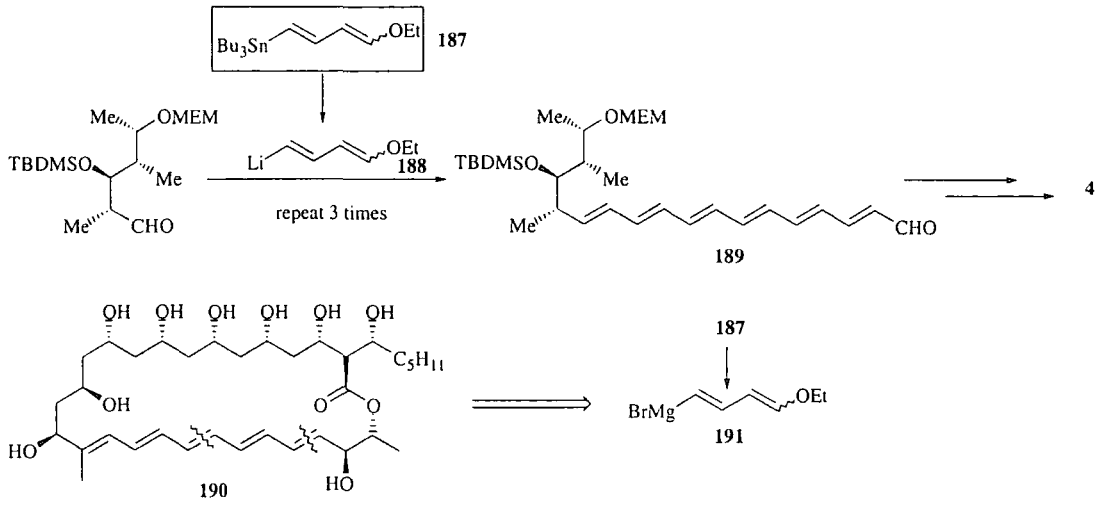
Scheme 35



Chemoselective acylation of bis(TMS) enyne **182** followed by enantioselective chemical reduction and catalytic hydrogenation of the triple bond leads to (*E*, *Z*)-diene **183** which is transformed into bromodiene **184**. A similar sequence applied to bis(TMS) acetylene gives **185** which undergoes hydroboration with catecholborane to generate a vinylic boronic ester *in situ*; Suzuki-Miyaura coupling of this with **184** affords, after deprotection, **186** in 41% yield.[91]

In a comparative study of several methods of polyene synthesis, including HWE strategies, an iterative strategy based upon the Wollenberg reagent **187**[92] was found to be superior for the synthesis of the hexaene section of amphotericin B **4** (scheme 36).[93] This reagent is readily prepared and undergoes transmetalation to give either the lithiated species **188**, or Grignard-type reagents such as **191**, used recently by Rychnovsky's group to install four of the five double bonds of Filipin III **190** (scheme 36).[94]

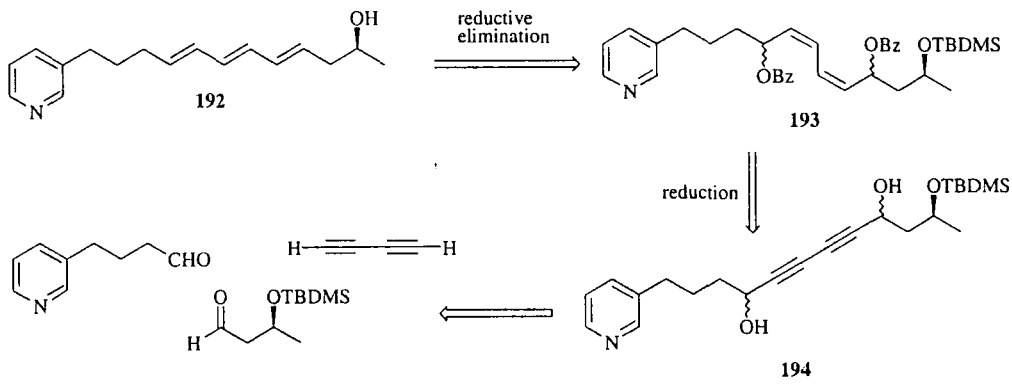
Scheme 36



Solladié's group have enjoyed much success using reductive elimination as a means of synthesizing polyenes in a stereoselective manner. Their strategy was recently exemplified by the first enantioselective synthesis of the alarm phermomone haminol-1 **192** (scheme 37). Diyne **194**, obtained through condensation of diacetylene with the appropriate aldehydes, yields the precursor dibenzoate diene **193** under standard conditions, with **192** attained as a single isomer following the reductive elimination step.[95]

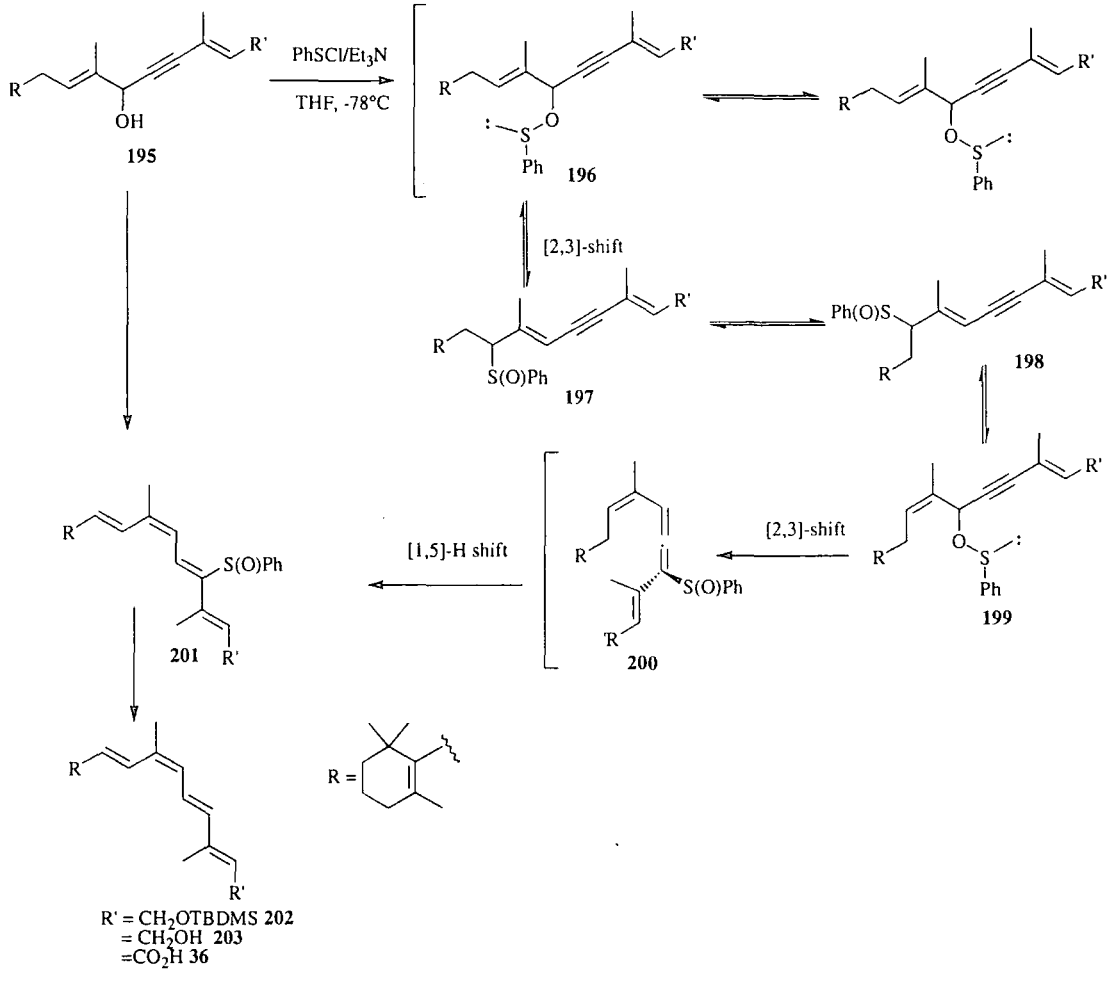
A pericyclic approach to the 9-*cis*-retinoids was recently put forward by de Lera and co-workers (scheme 38).

Scheme 37



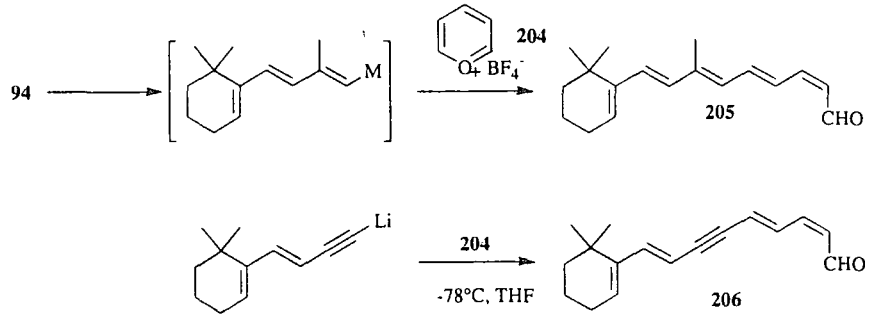
A domino sequence, involving a reversible [2,3]-allyl sulfenate to allyl sulfoxide rearrangment (**196-197**), followed by propargylic sulfenate to vinyallene sulfoxide rearrangment (**199-200**), and finally, an irreversible, doubly stereoselective [1,5]-hydrogen shift to give **201**. Desulfuration according to Okamura, and deprotection, affords 9-*cis*-retinoids **36** and **203**.[96]

Scheme 38



Taylor's group have used pyrylium salts to effect polyene synthesis; treatment of pyrylium tetrafluoroborate **204** with suitable organometallics allows access to a variety of retinoids, including the novel dehydro-demethyl-retinoid **206**.[97] (scheme 39)

Scheme 39



Conclusion

As can be seen from this review, much progress has been made in the area of polyene natural product synthesis over the last 30 or so years, and new methodology is constantly emerging. However, the ability to reliably construct polyenes with absolute control over alkene geometry, particularly for those systems possessing *cis*-alkenyl

units, remains an elusive goal. The increasing usage of polyene natural products in medicine, as drugs and as biological probes, as well as the general interest in polyenes for other applications, *e.g.* non-linear optics, should serve to fuel the continuing interest in this area, and help to achieve this goal.

2.0 Results and Discussion

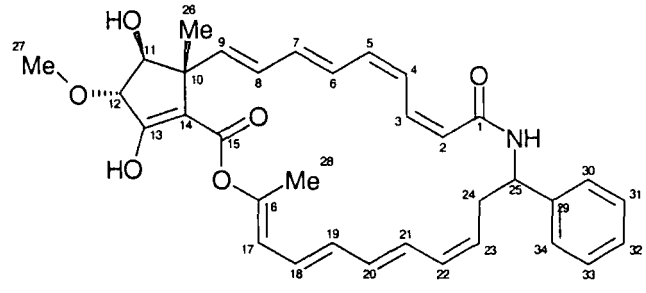
2.1 Aims and overview of the project

As is hopefully evident from the introductory literature survey, there is still a requirement for a procedure able to reliably construct polyene systems in a mild, high yielding and highly stereoselective manner. As has already been mentioned, work carried out in these laboratories, building on methodology developed specifically to overcome this shortfall[75, 98] has successfully demonstrated that a protocol employing a vinylboronate (functioning as a vinyl dianion equivalent) can be used to construct sensitive polyenes with a high level of stereoselectivity; this was exemplified by the recent synthesis of phthoxazolin A **133** (see section **1.8**, scheme 21 and onwards).

Although the assembly of this natural product was far from trivial and its (*Z, Z, E*)-triene moiety posed a significant trial of this new methodology, it was felt that a more challenging candidate for total synthesis should be sought as a definitive test. A formidable target having the requisite mixed geometry conjugated polyene moieties is found in viridenomycin **11** (see fig. 2), a bacterially derived polyene macrolide, and it is the explorations into the stereoselective total synthesis of viridenomycin that will be presented in this thesis.

2.2 Biological activity and structural considerations of the target viridenomycin.

Figure 9. Structure of the polyene macrolide antibiotic viridenomycin



Viridenomycin, shown in fig. 9 and annotated with the numbering system adopted in the paper first reporting its isolation and characterisation,[17] is a novel 24-membered macrocyclic polyene lactam. During the course of a screening program carried out in 1990 to find new antitumour antibiotics, a compound was isolated that

was found to prolong the survival period of mice afflicted with B16 melanoma cells. The compound was designated AL081 after the strain it was isolated and cultured from, and on the basis of physiological and morphological features, strain AL081 was itself classified as belonging to the genus *Streptomyces*. It was noted that the properties of strain AL081 were concordant with many of those exhibited by *Streptomyces gannmycicus*, and thus the eponymic compound AL081 was imputed as a metabolite of this bacterial species. Structural elucidation of compound Al081 was sought, and brought forward an interesting finding from preliminary investigations. Table 7 shows a comparison between some physico-chemical properties of AL081, and another compound isolated and reported by the same group sixteen years previously, termed viridenomycin.

Table 7

	Viridenomycin	**AL081**
Appearance	Colourless fine plates	White powder
Melting point	168-170°C (dec)	185-190°C (dec)
$[\alpha]_D$	+893 (32°C, c 0.5 in $CHCl_3$)	+195 (25°C, c 0.5 in $CHCl_3$)
UV λ_{max} nm (in MeOH)	310	309
MW (m/z)	566 (vapour pressure osmometry)	556 (FD-MS, MH^+)
Elemental analysis:		
Found:	C 72.09 H 7.01 N 2.42 O 18.48%	C 73.58 H 6.56 N 2.42 O 17.44%
Calculated:		C 73.49 H 6.71 N 2.52 O 17.28%
Molecular Formula	$C_{34\text{-}36}H_{35\text{-}41}NO_{6\text{-}7}$	$C_{34}H_{37}NO_6$

In light of these interesting similarities, the structures of both compounds were investigated more closely using a variety of spectroscopic techniques, with the final structures being determined using two-dimensional NMR methods. It was at this point that is was ascertained that AL081 and viridenomycin were one and the same compound, as testified by direct comparison, with both structures having physico-chemical and spectroscopic properties fully consistent with the compound shown in figure 9, hereinafter referred to as viridenomycin. Viridenomycin had first been isolated from the culture broth of *Streptomyces viridochromogenes* as a weakly acidic and lipophilic compound which had strong inhibitory activity against *Trichomonas vaginalis* and certain gram-positive bacteria, but no anti-tumour activity had been described at the time. The activity of viridenomycin against murine tumours (table 8) demonstrated in the later study showed that it possessed a wealth of biological activity, and it is this

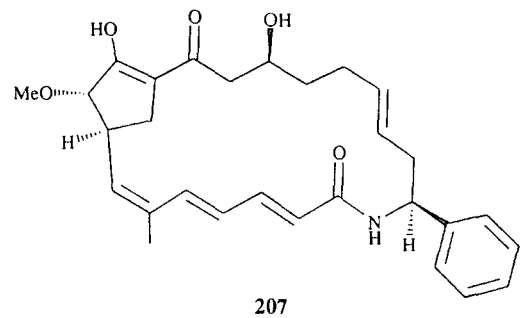
activity, together with its challenging structural features, that make viridenomycin an appealing candidate for total synthesis.

Table 8, showing the increases in life span (ILS) attributed to intraperitoneal inoculations with viridenomycin

Dose (mg / kg. / day)	P388 leukaemia		B16 melanoma	
	Survival days	ILS (%)	Survival days	ILS (%)
0	9.2 ± 0.42		14.7 ± 0.75	
5	11.3 ± 1.37	23	20.1 ± 1.15	37
10	Toxic		Toxic	

Viridenomycin is classified as a 24-membered polyene macrolide antibiotic, containing both a lactam and enol lactone linkage. It features a *(Z,Z,E,E)*-tetraene in the northern hemisphere(C_2-C_9) and an *(E,E,E,Z)*-tetraene in the southern hemisphere (C_{16}-C_{23}). Other salient structural characteristics include a tetrasubstituted β-ketocyclopentane carboxylic acid substructure, which was shown by spectral means to exist in the enol form as drawn in figure 9. Also of note is that C_{10} in the cyclopentane ring is asymmetric and quaternary, and the stereochemistry at C_{25} (a constituent of the C_{23}-C_{25} moiety which biochemically evokes a β-phenylalanine derived pathway) is unknown (this will be discussed in **2.3.4**). The cyclopentenol moiety alone makes viridenomycin an interesting target for total synthesis, but it was predominantly the construction of the awkward polyene units, which should thoroughly test the palladium coupling methodology developed in the group, that was of principal interest. A further point of interest concerning viridenomycin is its structural similarity to another *Streptomyces* metabolite, hitachimycin **207**, shown in fig. 10. Hitachimycin, a compound which has been synthesized and whose structure has been fully elucidated by comparison to the natural compound,[99] is a novel 19-membered macrocyclic anti-tumour antibiotic, and although lacking the tetraene systems and ester linkage of viridenomycin, the environment of its phenyl ring and its cyclopentene tether reveal pronounced structural similarities.

Figure 10. Structure of hitachimycin **207**



207

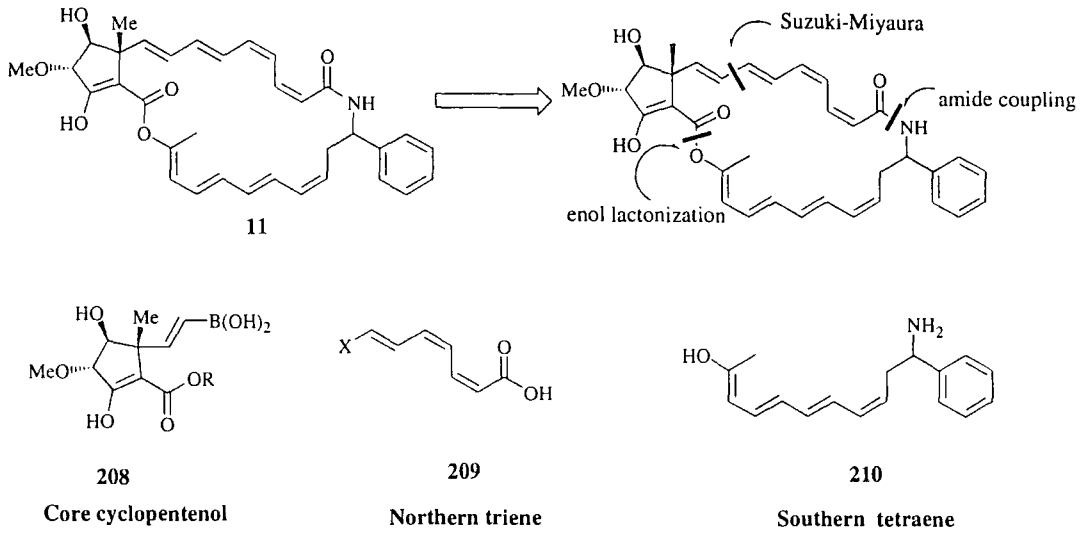
2.3 Retrosynthetic analysis of viridenomycin.

During the studies into the isolation, biological evaluation and structural elucidation of viridenomycin, it was observed that the compound appeared particularly unstable, having a half-life of only a few hours even when stored below 0 °C under an inert atmosphere. This is most probably due to the chemical, thermal and photosensitivity of the polyene regions, and it would have been remiss to ignore these sensitivities when performing a retrosynthetic analysis. We were thus mindful of the fact these sections might pose the greatest problems in the synthesis, and accordingly we decided on an approach that would allow these polyene sections to be assembled in isolation. Three disconnections seemed obvious and satisfied the requirements suggested by the aforementioned considerations; these are shown below in fig. 11 and naturally lead to three fragments: a core cyclopentenol, the northern (*E, Z, Z*)-triene (C_2-C_9), and the (*E, E, E, Z*)-tetraene of the southern hemisphere (C_{16}-C_{23}).

The key stages of rebuilding the macrocycle during the forward synthesis would then entail a Csp^2-Csp^2 Suzuki-Miyaura cross-coupling across C_7-C_8, amide bond formation to reinstall the C_1-C_{25} linkage, and an enol lactonization to anchor the southern tetraene **210** to the cyclopentenol tether **208**. This raised the question of which of these particular ring-closing bond formations to make the final macrocyclization step, and additionally, the reliability and functional group tolerance of the palladium cross coupling reactions also meant it would no doubt be possible to apply them to the macrocyclization step; this allows for a flexible retrosynthetic strategy featuring disconnection across any one of the Csp^2-Csp^2 bonds *i.e.*, the so-called "stitching" technique mentioned in section **1.8**, and illustrated in scheme 15.

An alternative approach, with considerable literature precedent, would be to make the final ring-closure step a macrolactonization.

Figure 11. Retrosynthetic analysis of viridenomycin **11**.



2.3.1 Macrolactonization techniques

There are several problems with this strategy that should be mentioned, firstly, the large negative entropy associated with large-ring cyclizations means that very high reactivity is required in the ester-forming reaction. Secondly, the reactions need to be performed at high dilution, to prevent the occurrence of intermolecular ester formation. High dilution can cause problems in itself, and since high dilution is often achieved through slow addition of one reagent to a reaction-causing mixture, special design of reagents and highly reactive intermediates are required. Nevertheless, these problems can and have been circumvented, and consultation of the literature reveals that macrolactonizations have successfully been applied to a number of macrolide antibiotics and a number of reliable protocols exist by which to perform them.

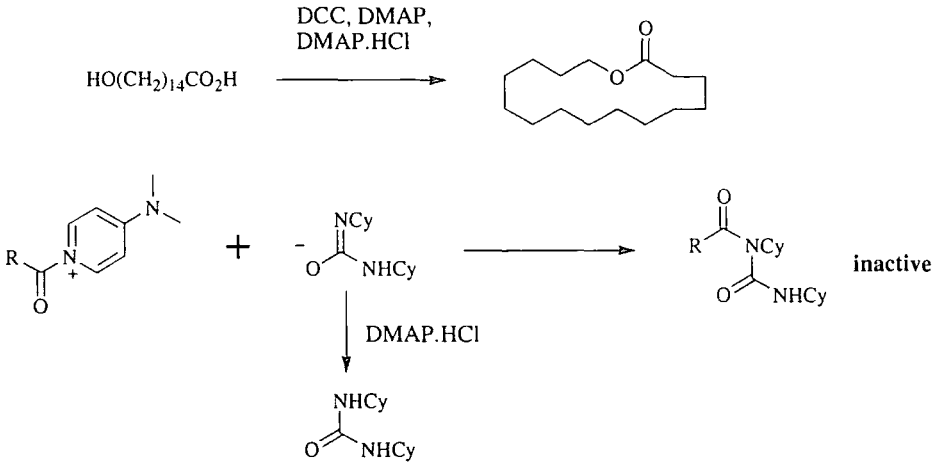
2.3.1.1 Carbodiimide techniques

Representative of these techniques are the methods developed by Keck[100] which can be applied to the formation of large-ring lactones. One problem encountered here is the incidence of side reaction of the activated acylpyridinium intermediate; this is especially evident at high dilutions, as at normal concentrations reaction with the alcohol would be fast. For this reason, DMAP-HCl is a requirement (see scheme 40).

2.3.1.2 Double activation methods

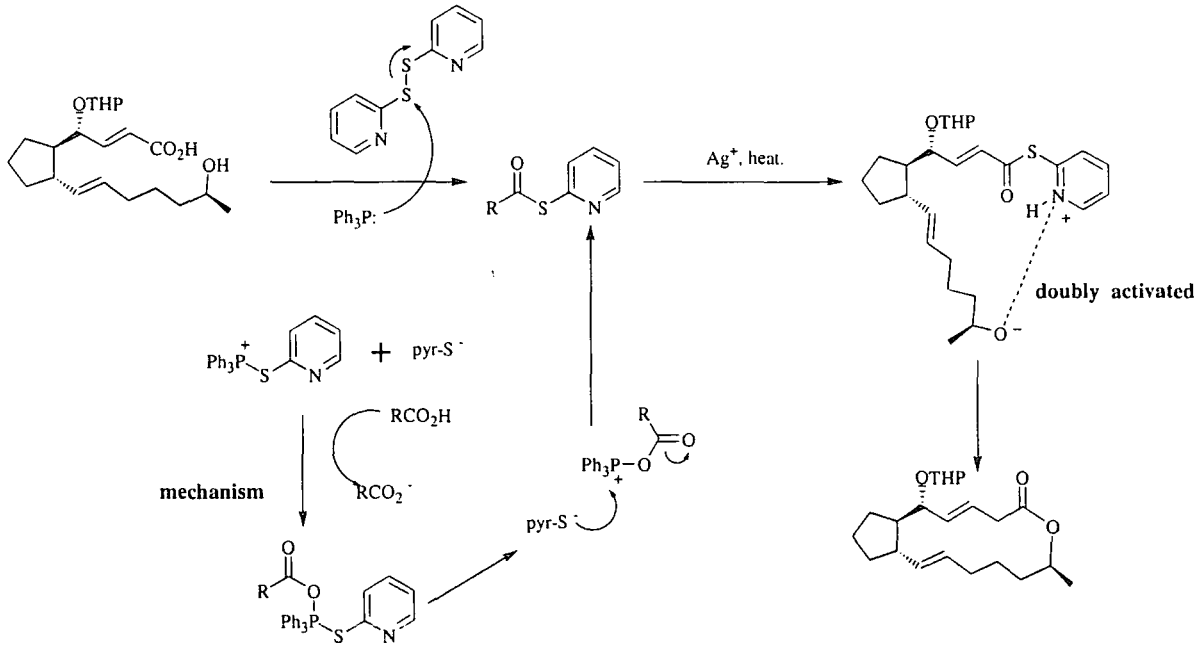
This strategy was originally presented by Corey and Nicolaou[101] who developed it specifically for macrolide formation. The acyclic precursor is viewed as a ω-hydroxy acid in which the carboxyl function is activated as a 2-pyridinethiol ester.

Scheme 40



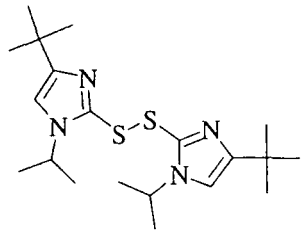
Proton transfer from the hydroxyl group to the pyridine nitrogen activates the hydroxyl as the alkoxide, and encourages hydrogen bonding between the charged oxygen and nitrogen, supposedly aiding intramolecularity (scheme 41).

Scheme 41



Variations on this approach have appeared, including the use of more efficient reagents to effect formation of the thioester, such as the imidazoyl derivative[102] shown in figure 12.

Figure 12. Imidazoyl-derived thioester.

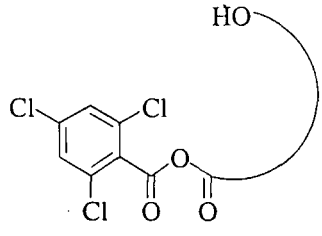


Silver(I) salts are also employed to speed up the reaction, presumably through coordination to sulfur. These modifications allow the reactions to be performed at lower temperatures, and can offer higher yields.

2.3.1.3 Mixed anhydride methods

Activation of carboxylic acids as mixed anhydrides has proved to be an effective way to achieve lactonization. For example, in Yamaguchi's syntheses of methynolide and neomethynolide[103] the lactonization was achieved using 2,4,6-trichlorobenzoyl chloride (figure 13).

Figure 13



Inorganic mixed anhydrides have also proven to be effective, as in Masamune's synthesis of narbonolide, in which the carboxyl group is converted to the phosphoric acid mixed anhydride through treatment with diphenyl phosphochloridate.[104] This strategy requires lower temperature (less than 80 °C), since the intermediate phosphoric acid anhydride is unstable towards heat and prone to disproportionate.

2.3.1.4 Mitsunobu method

The Mitsunobu method[105] allows the formation of medium and large ring lactones under mild, neutral conditions, using standard Mitsunobu reagents and conditions.[106]

2.3.2 Macrolactonization of viridenomycin

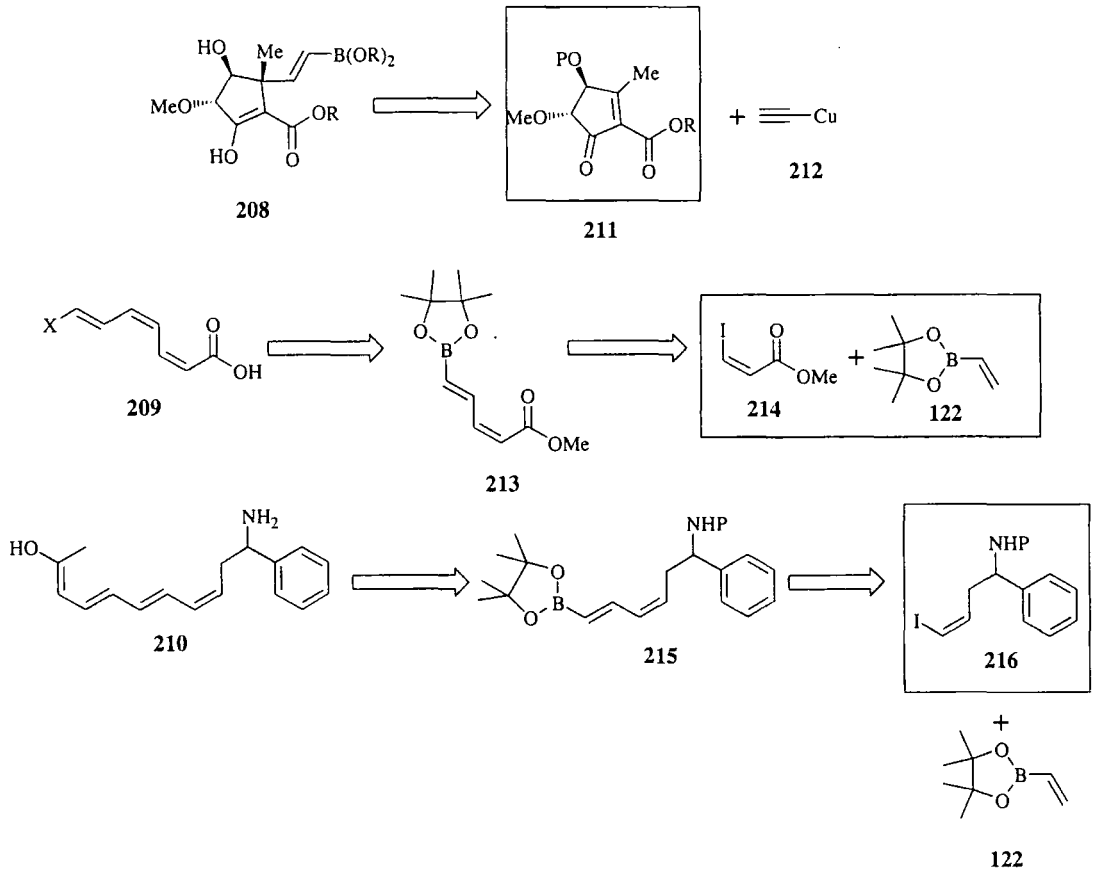
The spectroscopic data for viridenomycin indicated that the lactone linkage is in fact an enol-lactone linkage; hence, we would need to perform an enol-lactonization.

Fortunately, there is literature precedent for this as both acetyl chloride and isobutyl chloroformate have been used successfully to generate mixed anhydrides which undergo cyclization to give enol-lactones.[107] The cyclization step is obviously extremely important, and needed special regard considering the certain sensitivity of the acyclic precursors. For this reason, the idea of employing other methods such as the C_1-C_{25} lactamization to ultimately close the ring was also entertained fairly early on in the project.

2.3.3 Approaches to the major fragments

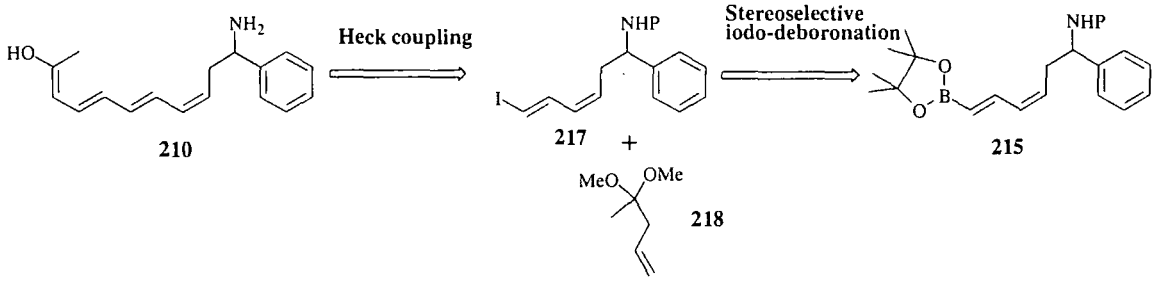
As mentioned above, the retrosynthetic disconnections cleaved viridenomycin into three pieces, and by and large, these three pieces, each requiring widely varying chemistry to assemble them, naturally divide the discussion presented here into three major sections: efforts directed towards the synthesis of the core **208**; towards the northern triene **209**, and towards the southern tetraene **210**. Although more detailed retrosynthetic analysis will be presented in the forthcoming sections that deal with each of these particular fragments, it is pertinent to give a broad outline of the strategies towards them first (fig 14).

Figure 14. Outline retrosynthetic analysis of the major fragments.



The approach to be taken was to attach the northern tetraene **209** to the core **208** by means of a Suzuki-Miyaura coupling, a strategy requiring an alkenyl boron and an alkenyl halide partner. It seemed sensible to assume that a chelate-assisted Michael addition of a suitable acetylenic metal species (we envisaged a lithium organocuprate being ideal for this) to the enone precursor **211**, followed by hydroboration of the alkyne functionality with catecholborane should provide us with **208**, the requisite alkenylboron species, whilst it was imagined that it would be able to construct the halide partner through initial coupling of iodoacrylate **214** with vinylboronate **122**, providing Heck diene **213**; subsequent stereoselective iodo-deboronation of **213** (see **2.4.1.3** for details of this procedure) should provide **209**. Similarly, Heck coupling of **122** with the protected iodoamine **216** should give dienylboronate **215** (fig. 15). Stereoselective iodo-deboronation to afford iodide **217**, and Heck coupling of this with alkene **218** should provide us with **210**, after unmasking of the carbonyl functionality.

Figure 15. Assembly of the southern tetraene



210 **217** + **218** **215**

2.3.4 The problem of absolute configuration.

The absolute configuration of viridenomycin is not known. During the studies carried out by Nakagawa and co-workers that established the structure of viridenomycin, the stereochemistry at C_{25} were never determined, and thus there was the significant problem of not knowing which enantiomer of **216** was required to produce the biologically active diastereomer of viridenomycin. In the absence of an authentic sample of viridenomycin to probe spectroscopically or by chemical means, it was necessary to look towards molecular modelling to determine which configuration at C_{25} was more favourable on energetic grounds, and also to the literature, to compounds having similar structural features to viridenomycin, given that the particular section incorporating the stereocentre of unknown configuration was likely to have been derived from β-phenylalanine. Interestingly, there was another natural product that

showed certain homology with viridenomycin that provided a clue as to which enantiomer was more likely and it has already been mentioned in section **2.2.**

(+)-Hitachimycin **207**, fig. coupling of this with alkene, is a macrocyclic antitumour antibiotic independently isolated in the early 1980's by Omura and Umezawa.[99a-b] The Omura group focused primarily upon structure elucidation using chemical degradation, NMR techniques, and biosynthesis experiments using ^{13}C labelled precursors. Although they were able to deduce the bulk structure, the absolute stereochemistry at two of the four stereogenic centres remained undefined. Ten years later, Smith and co-workers defined the complete relative and absolute stereochemistry, as well as the solid-state and solution conformation of (+)-hitachimycin, using two-dimensional NMR spectroscopy, single crystal X-ray analysis, and computational methods.[99c-d] They then followed this with the first reported total synthesis.[99e]

The absolute stereochemistry at C_{21} of hitachimycin has been confirmed as (*S*), both from ^{13}C labelling and X-ray crystal analysis, and it is believed that the β-phenylalanine moiety is incorporated *via* a polyketide pathway, with the natural α-amino acid (*S*)-phenylalanine being converted through the action of an amino mutase enzyme. By analogy, it was postulated that the absolute stereochemistry at C_{25} of viridenomycin (also possessing this β-phenylalanine moiety) is also (*S*), being derived from a natural α-amino acid in a similar fashion. To test this hypothesis, we carried out some preliminary modelling[108], forcing both (R) and (*S*) stereochemistries at C_{25} in order to compare energy differences between the two minimized conformers. Unfortunately, although the (*S*)-form gave the lowest energy conformer, the computer calculated coupling constants for H_{24a} - H_{24b}, H_{25} - H_{24a} and H_{25} - H_{24b} (see fig. 16) differed significantly from the values obtained experimentally in the original paper (table 9). The calculated coupling constants for the higher energy (*R*) conformer showed even greater deviance from those derived experimentally.

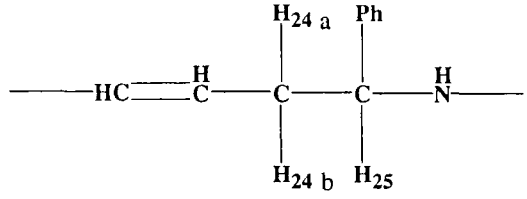
Table 9: Comparison between experimental and predicted ^1H-^1H coupling constants around C_{25} of viridenomycin.

Proton's coupling	$J_{experimental}$, Hz	$J_{predicted}$, Hz.
H_{24a}-H_{24b}	13.5	14.0
H_{25}-H_{24a}	3.5	4.5
H_{25}-H_{24b}	4.5	11.5

This suggested either that the modelling was inaccurate, or that the original paper had incorrectly reported these coupling constants. To verify this, we contacted the research

group who reported the characterization of viridenomycin, but they gave assurance that the data was correct.

Figure 16



This assurance prompted continued efforts to try to solve this problem using modelling, but by adopting a slightly different approach. The dependence of ^3J coupling constants on the dihedral angle θ for a H-C-C-H fragment is represented by the Karplus equation (equation 1). Although the expression produces a well-defined cosine function, the actual range of experimental values of *J* often shows discrepancies of up to 4 Hz compared with the calculated values, producing the 'envelope' shown in figure 17 when plotted against θ as opposed to a discrete curve, and hence the empirical constants A, B and C, having values 7, -1, and 5 respectively, were introduced to attempt to correct for this.

Equation 1

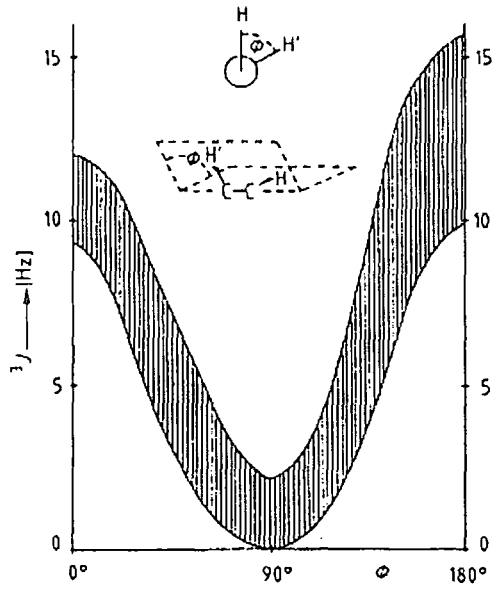
$$^3J = A + B\cos\theta + C\cos 2\theta$$

The second approach taken thus aimed to solve the equation for the values of ^3J presented in the original characterization paper (table 9), which were obtained from two-dimensional NMR analysis. Solutions to equation 1 yield two values for θ in the range $0 \leq \theta \leq 180°$, thus giving two possible dihedral angles for each value of *J*. At this point of the project we participated in a brief collaboration with Peter Coveney's computational group at Queen Mary College, London, and they applied Monte Carlo conformation searches using the AMBER forcefield[109] (which is one of the more reliable forcefields when dealing with large biomolecules) to both diastereomers of viridenomycin, before using DFT methods to further optimise each lowest energy conformer. The H_{24a}-C-C-H_{25} and H_{24b}-C-C-H_{25} dihedral angles were then measured from the models, and compared to those obtained from the Karplus equation calculations. Unfortunately, no obvious correlations were apparent, and the results of this study were thus inconclusive. Interestingly however, Coveney's group tried a number of different approaches using the original strategy, which attempted to correlate computer calculated *J* values to those obtained experimentally, and they obtained much

the same result as had been found before: the diastereomer having the (*S*)-configuration at C_{25} did indeed have a slightly lower energy than its (*R*) counterpart.

Because the modelling studies had failed to establish conclusively which of the two diastereomers best matched the data presented in the characterization paper, we

Figure 17. Karplus plot showing the relationship between the vicinal coupling ^3J and the dihedral angle.



were forced to consider that either the modelling was wholly inaccurate, or the data reported was actually incorrect. The former is a possibility; even those force-fields better suited to modelling more complex biomolecules are not optimized for polyenic systems; they show a tendency to force an overall flat conformation on molecules such as viridenomycin; nevertheless, the fact that ourselves and Coveney's group produced duplicate results using different modelling packages and force-fields, both suggesting that the (*S*)-C_{25} diastereomer was the more energetically favourable one, hints that the modelling may not be all that unreliable after all. The latter consideration, that the NMR data had been reported incorrectly despite the assertion otherwise, is impossible to verify in the absence of an authentic sample.

Because of these difficulties and the lack of an obvious solution, there was little choice but to proceed with the synthesis, making the assumption that the configuration at C_{25} was (*S*), based on reasons stated earlier; and thus we initially sought to prepare the (*S*) enantiomer of **216**.

2.4 Synthetic efforts towards viridenomycin.

2.4.1 Routes towards the southern hemisphere tetraene 210

A pivotal synthon in our strategy to construct **210** was the iodoamine **216**. It can safely be said that more effort was directed towards the synthesis of this one seemingly trivial compound than towards any other single area of the project! A multitudinous host of methods were employed to elicit the preparation of (*S*)-**216**, which can be loosely grouped into three main areas according to the manner in which we attempted to install the asymmetric centre: firstly, by asymmetric reduction of an oxime ether according to Itsuno's methods; secondly, by asymmetric alkylation of an imine under phase-transfer conditions; and thirdly, and the strategy that proved most successful, by starting from a compound having the required stereochemistry already in place, in this case, from an amino acid. Because it roughly approximates to the chronological sequence of events that went into finally constructing **216**, the discussions into the preparation of **216** will be presented in this self-same order.

2.4.1.1 Strategy 1: Installation of the C-25 stereocentre by asymmetric reduction of an oxime ether (Itsuno reduction)

Figure 18 shows all avenues explored in order to arrive at **216**, or more precisely, routes taken to attempt to produce the requisite oxime ethers needed for asymmetric reduction. Although this retrosynthetic tree illustrates the convergent approach taken, not all routes suggested by it were pursued; as such, it represents both possibilities that could have been explored, as well as actual synthetic routes that were pursued. Although each of the avenues taken towards **216** start at different compounds and utilize different chemistry, they all have one thing in common, namely, the stereoselective reduction of an oxime ether as the means by which the (*S*)-stereochemistry is introduced.

In 1985, Itsuno described the stereoselective reduction of ketones and ketoxime *O*-alkyl ethers with reagents prepared from borane-THF or borane-DMS complex and chiral vicinal amino alcohols, with the best results being obtained from the reduction of acetophenone *O*-methyloximes employing chiral oxazaborolidine **225**, known now as Itsuno's reagent.[110] (fig. 19)

Figure 18. Retrosynthesis tree showing routes taken to reach (*S*)-**216**

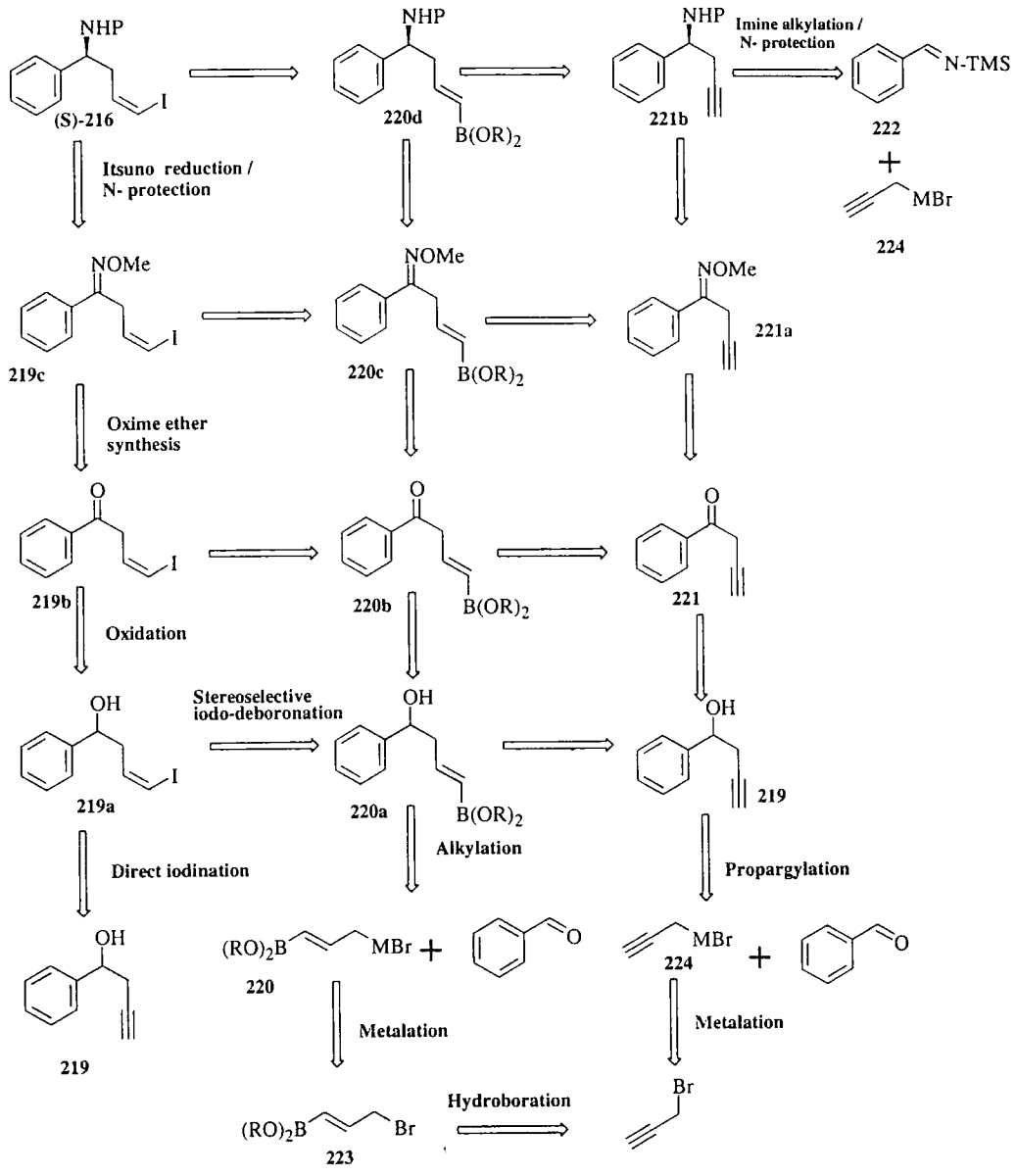
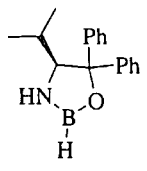


Figure 19. Itusno's reagent.



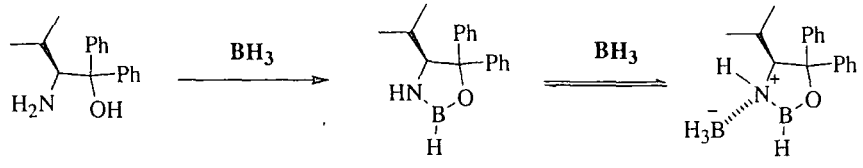
225

Itsuno found that reductions carried out using reagents mixtures having a 1:2 molar ratio of amino alcohol to borane gave the highest degree of selectivity (up to 99 % *ee*.), whereas 1:1 mixtures gave disappointingly low results.

In related work into the asymmetric reductions of ketones, Corey discovered that mixing a suitable chiral alcohol with two equivalents of borane gave a rapid reaction,

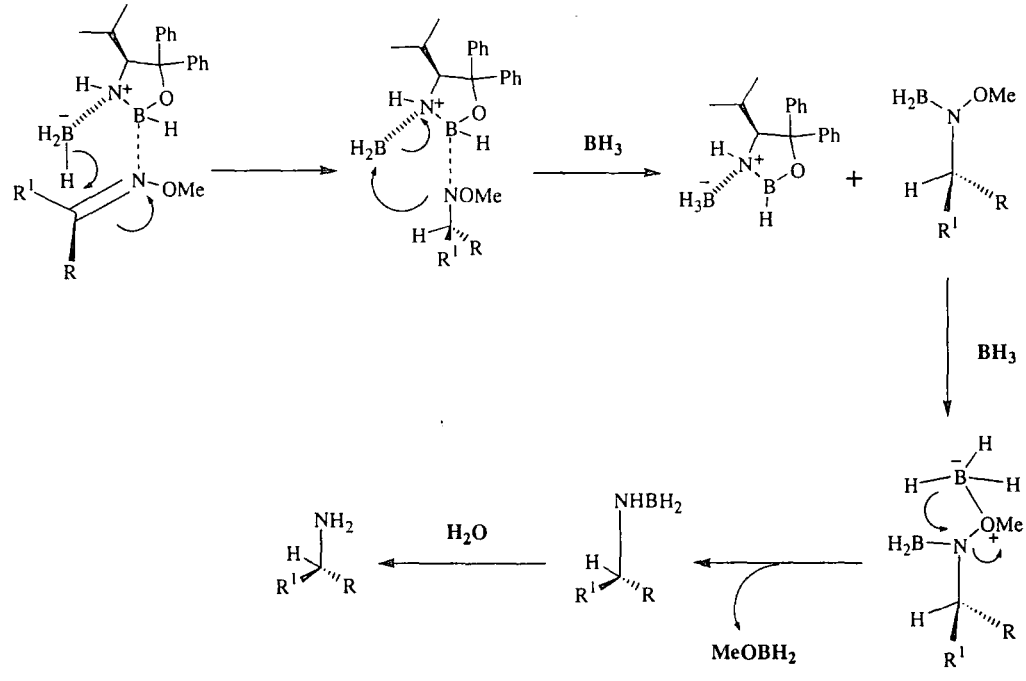
liberating two equivalents of hydrogen and forming the oxazaborolidine **225**.[111] He found that although **225** itself did not reduce ketones directly, 1:1 mixtures of **225** and borane effected total reduction of acetophenone at rates comparable to those obtained using Itsuno's mixtures. ^{11}B NMR analysis of 1:1 mixtures of **225** and borane clearly indicated an active reducing species consistent with that shown in scheme **42**, structure **226**, and a postulated mechanism for the reduction of ketoxime *O*-alkyl ethers, analogous to that used to explain the asymmetric reduction of ketones using similar chiral oxazaborolidines, is shown in scheme **43**.

Scheme 42



225 **226**

Scheme 43



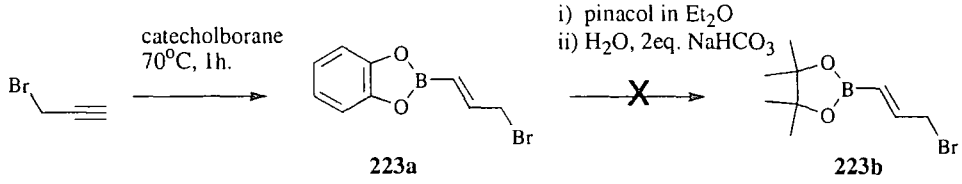
Given the usually impressively high yields and selectivities afforded by Itsuno reduction, and the experience within the group imparted through prior successful application of this methodology,[112] it was felt that this would be an ideal way to introduce the required stereochemistry into iodoamine **216**, and accordingly efforts were directed towards preparing suitable Itsuno substrates.

Early efforts to this effect commenced with hydroboration of propargyl bromide to give compounds of type **223**, with a view to generating an organometallic species **220**

capable of alkylating benzaldehyde in order to give alcohols **220a**, or iodoalcohol **219a** following stereoselective iodo-deboronation. Oxidation of such an alcohol should then provide ketones **219b** or **220b**, which should then be readily converted into the necessary oxime ethers **219c** or **220c**.

Treatment of an 80% solution of propargyl bromide in toluene with neat catecholborane[113] (CBH) for 1h at 70 °C gave **223a** in good yield (scheme 44).

Scheme 44



223a **223b**

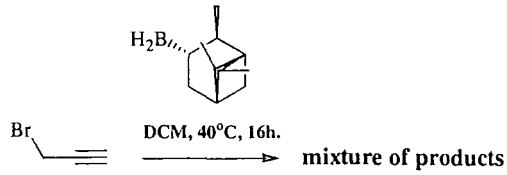
90%

Due to the propensity of such catecholboranes to undergo proto-deboronation under even mildly acidic conditions (for example, during silica gel chromatography) and their sensitivity towards moisture,[114] it was decided to attempt to trans-esterify **223a** to the more hindered and thus more stable pinacol ester **223b**,[115] employing standard conditions which had previously been found successful.[116]

Unfortunately, in every instance, yields were extremely low, with boronic acid being isolated as the major product. The suspicion was that this could have arisen during the acidic work-up following transesterification, but even when this was omitted and replaced by thorough washes with water, the result was still the same. A possible and tentative explanation is that the catechol liberated during the transesterification process is sufficiently acidic itself to effect proto-deboronation of **223b** as soon as it forms, resulting in the isolation of its hydrolysis product; the water solubility of the latter also may account for the low yields.

Suspecting the problem may be down to the choice of hydroborating agent, it was elected to try monoisocampheylborane ($IPCBH_2$). Disappointingly, the use of the 1:1 complex with TMEDA gave poor results under typical conditions (equation 2). This gave cause to seek an alternative to either CBH or $IPCBH_2$.

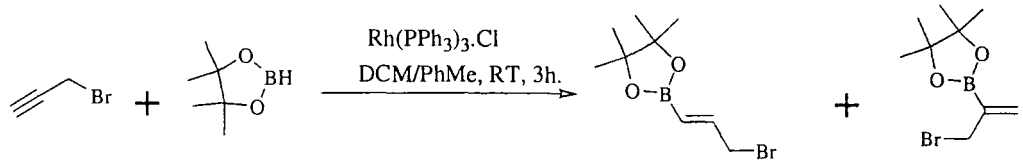
Equation 2



Since a stable pinacol boronic ester was desired and problems had been encountered previously in trying to perform the transesterification to reach this ester, the possibility of using pinacolborane (PBH) directly was examined. Initial reports of this reagent's utility by Knochel showed that PBH added rapidly to alkynes with excellent regio- and stereo-selectivity, and under very mild conditions (25°C, several hours).[117] Additionally, the derived alkenyl pinacolboranes can be purified by flash chromatography with no appreciable decomposition. The only disadvantage of this procedure was that a full two equivalents of PBH were needed to effect complete reaction, and unlike CBH, the reaction required solvent otherwise regioisomers were produced. By way of an improvement of this procedure, Srebnik and co-workers developed a transition metal catalyzed variant of this reaction, initially employing zirconocene $Cp_2Zr(H)Cl$ as catalyst.[118] Although the results were good, the incompatibility of this zirconocene with many functional groups spurred them to seek an alternative catalyst, and it was found that rhodium and nickel gave excellent results, enabling ready access to either terminal or internal alkenyl pinacolboranes. Although at the time propargyl bromide had not been hydroborated under these conditions, the nearest suitable match in terms of functionality and outcome was propargyl chloride, where it was found that 1 mol % of $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) and 1.05 equivalents PBH gave a 40:60 mixture of terminal to internal alkene, in 99 % yield overall, whereas the catalyst $Rh(CO)(PPh_3)_2Cl$ gave similar yields but with improved regioselectivity (99:1 terminal to internal).[119]

Attempts to hydroborate propargyl bromide under these conditions were met with limited success. After first preparing pinacolborane according to the method of Knochel, attempts to effect hydroboration with the more esoteric and expensive catalyst $Rh(CO)(PPh_3)_2Cl$ were unsuccessful, whilst use of Wilkinson's catalyst gave the two regioisomers in roughly the inverse ratio of that reported to have been obtained from propargyl chloride, and in much lower yield (equation 3).

Equation 3



223b **223c**

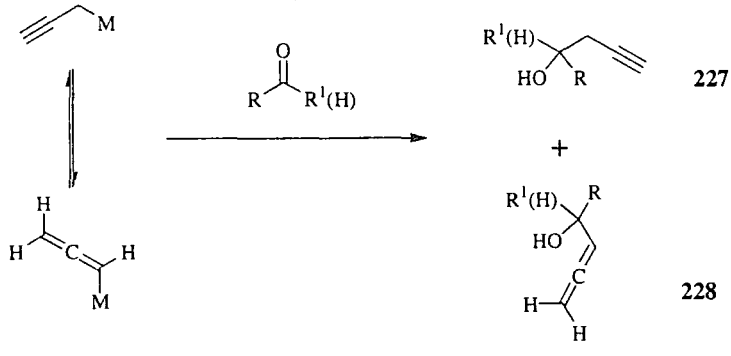
40 : 60
yield 58%

Because of this disappointing result, it was elected to change strategy and try a direct propargylation, with a view to introducing the triple bond intact to provide a homopropargylic alcohol such as **219** or **220a**.

Homopropargylic alcohols have proven utility in organic synthesis.[120] Amongst the techniques employed to prepare them, nucleophilic additions of propargyl- and allenyl-organometallics to carbonyls represents the most popular and reliable method.[121a]

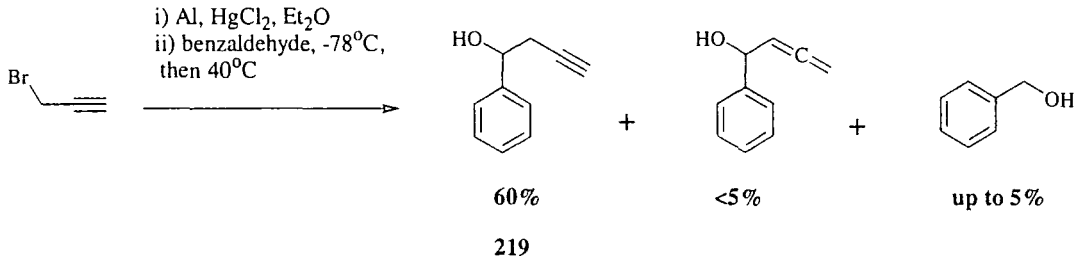
Such techniques are not without drawbacks however; in almost all cases, the problem of propargyl / allenyl tautomerization means that such nucleophiles lead to mixtures of homopropargylic and allenic alcohols **227** and **228**, with the metal's Lewis acidity, solvent effects, and steric hindrance between electrophile and metal substituents all effecting the overall regiochemistry (scheme 45).[121b-e]

Scheme 45



The first choice strategy was to employ a propargylaluminium species **224** (M=Al), generated through reaction of aluminium powder, mercuric chloride, and propargyl bromide, according to the method first reported by Guédin-Vuong for the preparation of homopropargyl ethers.[122]

Equation 4



In this method, a solution of propargyl bromide is slowly warmed with aluminium powder and catalytic mercuric chloride until the characteristic signs of metal C-H insertion are seen (effervescence, solution darkens in colour, aluminium powder was steadily consumed). It should be noted that without the mercuric chloride needed to 'clean' the aluminium surface of oxide, no reaction occured, and washing the aluminium powder with dilute acid first was insufficient as a means of activating it.
After gentle warming to complete the formation of the propargylaluminium species, the reaction is cooled to -78 °C and benzaldehyde added slowly, before the temperature is raised to complete the reaction. The problems encountered with this reaction are evident from equation 4.

Not only does the reaction yield the desired homopropargylic alcohol **219**, but allenic alcohol (as expected) and benzyl alcohol were also produced. Thinking that the latter had arisen by reduction, perhaps effected by some form of transitory aluminium hydride species formed during the metal insertion process, an inverse addition was performed, adding the organoaluminium reagent dropwise to the benzaldehyde-solvent solution so as to keep the concentration of any intermediate reducing species at a minimum, thus biasing the reaction towards propargylation. This strategy appeared to make little difference; with hindsight this is perhaps because the benzyl alcohol, which undoubtedly arises through reduction of benzaldehyde, was formed by action of aluminium amalgam, a reagent generated by the action of mercuric chloride on aluminium and which has been employed in the reductive amination of ketones.[123]
This method was fraught with other problems. Following work-up, besides the contaminants illustrated in equation 4, crude **219** contained a host of residual metal salts, particularly what is probably mercuric oxide judging by the deep red colour of the isolated product. Purification of **219** was attempted by vacuum distillation, but both **219** and benzyl alcohol co-distilled, and thus the two could not be separated. Attempts at chromatography were also unsuccessful as both alcohols had almost identical polarity

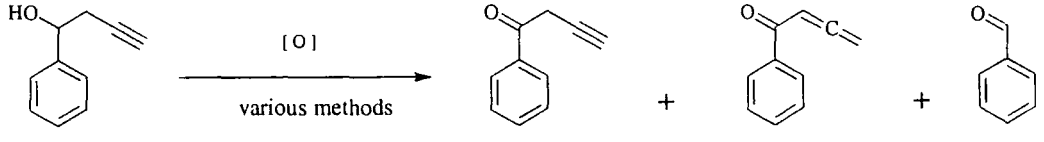
and co-eluted, and even this technique failed to thoroughly remove the metal contaminants. Alcohol **219** is a known compound, and although not fully characterized, the racemic form has been reported as being both a pale yellow oil and a white crystalline solid! A more recent paper suggests the latter is correct, with recrystallization from 1:1 hexane/ether affording **219** as a colourless solid.[124] However, in the absence of this information and with all attempts to purify **219** unsuccessful, it was opted to attempt to oxidise the mixture (after a preliminary distillation to remove the residual metal salts) to ketone **221a**.

The first four oxidation methods of choice utilized, Swern,[125] Dess-Martin[126] and PCC[127a] or PDC[127b] in DCM all proved highly efficient at oxidizing the trace benzyl alcohol back to benzaldehyde, yet left **219** untouched!

At the time this work was undertaken, there was only one instance of **221a** in the literature, where its synthesis from **219** was reported to have been achieved *via* Jones oxidation.[128, 129]

Although it was found that the procedure reported in this paper (which employed questionable quantities of dichromate and acid for the production of the Jones reagent) was unworkable, when the oxidation was attempted using a more contemporary preparation of the reagent, successful oxidation of **219** was achieved; unfortunately **221a** accounted for less than 10% of the product, with allenic ketone **229** present as a <5% contaminant, the major component being benzaldehyde. Two observations are worthy of mention: firstly, the amount of **229** recovered was entirely disproportionate with the amount of allenic alcohol present in the starting mixture, and secondly, if the reaction temperature was not maintained below 10 °C, the ratio of **229** to **221a** increased; both observations indicate the propensity of **221a** to rearrange to the more thermodynamically stable allene **229**.

Equation 5



219 **221a** **229**

less than 10% **less than 5%** **major product**

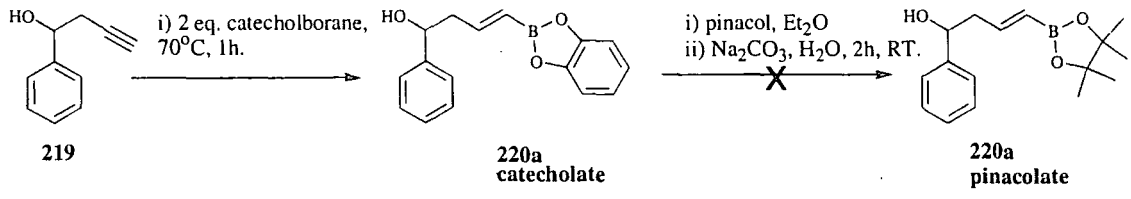
The benzaldehyde produced, the large amount of which could not have solely arisen from oxidation of benzyl alcohol, suggests oxidative cleavage of **219** under the somewhat abrasive reaction conditions.

This scenario (equation 5) thus conferred a mixture of three carbonyl compounds, with a choice of either attempting separation at this stage, or separating a mixture of three oxime ethers later on. To further confound the situation, the small amount of **221a** actually produced by the oxidation proved to be rather unstable on silica, and attempts to recrystallise or triturate it from the crude mixture were unsuccessful.

Because of the persistent problem of propargyl / allenyl tautomerization, no doubt biased towards the allenyl form in the case of **221a** due to conjugative stabilization, we investigated the possibility of taking out the triple bond *via* hydroboration prior to oxidation (giving **220a**), or by employing a direct approach to install the alkenyl iodide functionality early on (**219** → **219a**) *via* a process involving *in situ* generation of HI and anti-Markonikoff addition (this process will be discussed in more detail in section **2.4.2**).

The first attempt employed CBH, under similar conditions used previously for the hydroboration of propargyl bromide (equation **6**). Although the ^{1}H NMR spectrum of the crude reaction mixture indicated alkene resonances due to **220a**, the reaction appeared incomplete, and additionally, a mixture of uncharacterised compounds were clearly also being produced.

Equation 6



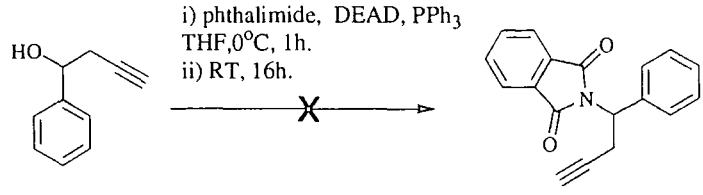
219 **220a catecholate** **220a pinacolate**

Attempts to transesterify **220a** under standard conditions once again met with failure, so transition metal mediated PBH hydroboration as tried earlier was attempted. Regrettably, this method also proved unsuccessful, as did attempts to synthesize **219a** by direct iodination; it was later discovered that this process is only successful when applied to acetylenic esters or acids.

Around this time, having largely thus far come up against several obstacles in attempts to prepare **216** *via* an oxime ether, a couple of methods to try to introduce the amine function early on were briefly examined. The first strategy was to employ a Mitsunobu reaction between **219** and phthalimide, with a view to then converting the

phthalimide **230** to the free amine by treatment with hydrazine, after which the enantiomers could be separated by kinetic resolution.

Equation 7



219 **230**

Unfortunately, although ^{1}H NMR spectroscopy indicated the presence of **230**, the reaction was generally rather messy (a condition probably exacerbated by the number of impurities in the starting material **219**), and this made attempts to isolate **230** all the more tedious.

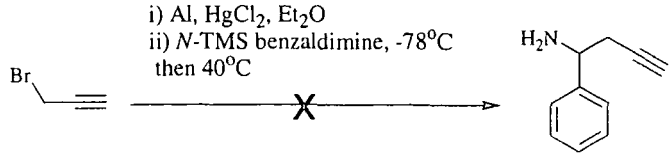
Since this was not a desirable set of circumstances so early on in the synthesis, it was decided to discontinue this approach and instead look at another means of achieving **216** by having the amine in place early on, namely, through an organometallic addition to an imine.[131]

Due to the weak electrophilicity of the azomethine carbon in imines, nucleophilic addition of organometallic reagents to C=N is often beset with problems such as competitive enolization, reduction, or coupling reactions. One solution to these problems is to activate the C=N bond towards addition through *N*-substitution; either with an electron-withdrawing group, or with a Lewis acidic metal, providing a metallo-imine.

This last approach seemed most appealing, as many of the commonly employed electron withdrawing *N*-substituents (for example, *N*-sulfonyl) are troublesome to remove; moreover, since it was desirable to utilize an aldimine, many of the *N*-substituents required to render these inherently unstable species stable carry the price of diminished overall reactivity towards C=N addition.[132]

Accordingly, *N*-TMS benzaldimine **222** was selected as the candidate electrophile, a reactive yet stable and easily handled metallo-imine readily accessed in good yields *via* a modified literature procedure.[133]

Equation 8

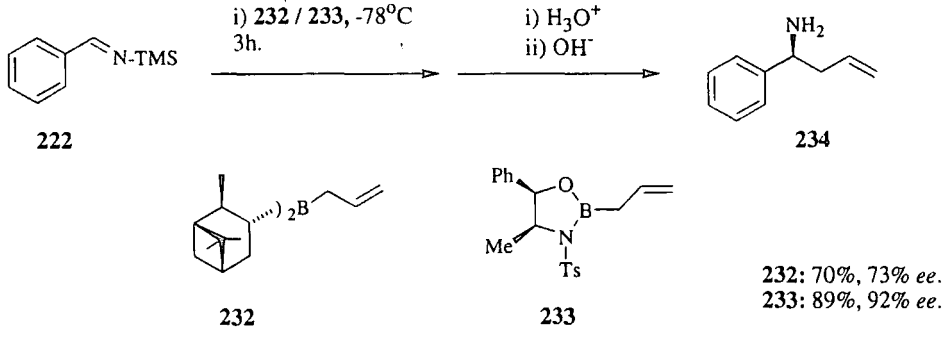


231

The first approach employed the propargylaluminium species **224** (M=Al) used previously with some degree of success, and the reaction was duly carried out in the same manner as illustrated in equation **8**. Unfortunately, this reaction led to a mixture of products, and the ^{1}H NMR spectrum of the crude reaction prior to work-up did not show obvious signs indicating the presence of **231**, instead mostly starting material **222** was evident.

A recent paper reported an interesting finding that gave cause to revisit this reaction later on in the project; in this paper, Brown and co-workers describe the critical importance of water in the asymmetric allylation of **222** by *B*-allyldiisopinocampheylborane **232**.[134] Curiously, and perhaps counter-intuitively given the instability of **222** towards moisture, they reported that unless one equivalent of water is added to the reaction, allylation did not take place, even after up to a week at room temperature! (scheme 46).

Scheme 46



222 **234**

232 **233**

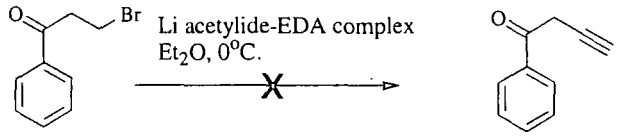
They posited that during the reaction, **222** functions as a 'masked' version of the reactive aldimine, liberated through reaction with water, and it is this free aldimine that rapidly reacts with the allylating agent. As a comparable reaction had been tried and it had been observed that the crude reaction mixture pre-work-up consisted largely of starting material, it was theorized that perhaps adding an equivalent of water to the reaction shown in equation **8** might induce formation of **231**, freeing the aldimine in a

similar manner, which should then react rapidly with the propargylaluminium nucleophile.

However, when this was tried, a complex mixture of products was obtained; although ^{1}H NMR spectroscopy indicated resonances attributable to both allenic and propargylic fragments, the presence of **234** could not be confirmed due to the number of components; furthermore, had **234** been present, isolation would have been laborious and the yield undoubtedly minute.

In light of these further setbacks, it was decided to re-investigate the route centred around preparation of the oxime ethers. First however, the possibility of side-stepping the problems encountered during the attempts to make **221a** using the troublesome propargylaluminium additions by introducing an acetylene unit directly was briefly examined (equation 9).

Equation 9



221a

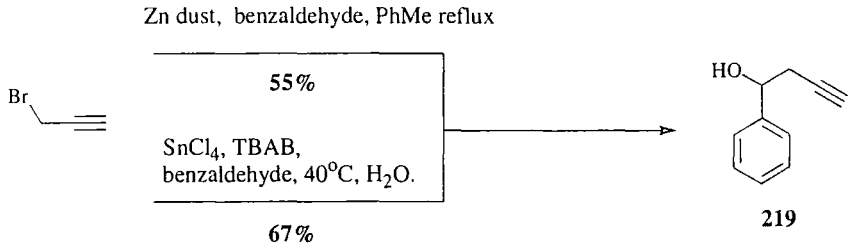
A convenient means by which to introduce an acetylene unit is *via* lithium acetylide, a moderately hard nucleophile available as a 1:1 complex with EDA. However, problems were consistently encountered with this reagent throughout the project, and when it was reacted with 2-bromo-1-phenyl-1-ethanone, only starting material was recovered.

It was next decided to try another method of preparing homopropargylic alcohol **219**, preferably one that would be cleaner than using the aluminium / mercuric chloride method since many of the problems encountered previously were probably due to the sheer number of contaminants (metals salts, by-products from side-reactions), and also one that would hopefully not give any of the unwanted allenic alcohol.

In the paper preceding that reporting the oxidation of **219** to **221a**, Henbest had reported the synthesis of β, γ-acetylenic carbinols *via* Reformatsky reactions with propargylic bromides (scheme 47).[135]

Although this reaction gave satisfactory results, the aqueous work-up advised gave rise to large quantities of voluminous zinc precipitates, necessitating repeated yield-diminishing filtration and making the reaction generally unpleasant to perform.

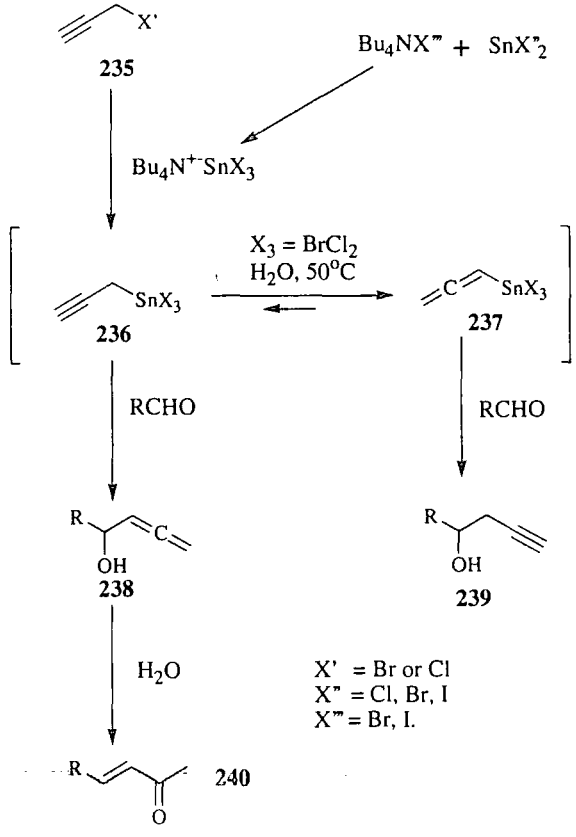
Scheme 47



It was discovered the most facile way to prepare **219** was *via* a tin-mediated process, as recently described by Masuyama and co-workers.[136]

The reaction, whose putative mechanism based upon ^1H NMR studies is shown in scheme **48,** shows marked dependence on both reaction medium and temperature.

Scheme 48

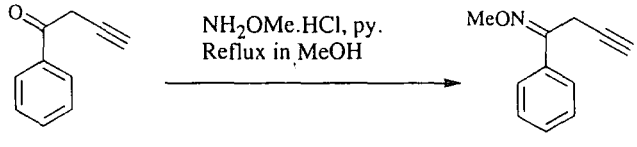


The hypothesis put forward is that reaction of propargyl chloride **235** (X=Cl) with tetrabutylammonium iodide and tin(II) iodide leads to the reactive species **236**, which in dry, polar solvents such as DMI and DMF, leads to carbonyl allenylation yielding **238**, and varying amounts of the hydration product **240**. Conversely, reaction of propargyl bromide **235** (X=Br) with tetrabutylammonium bromide and tin(II) chloride leads to **236**, but in aqueous media and at higher temperatures, rearrangement of **236** to **237** is faster than carbonyl allenylation, leading to homopropargylic alcohol **239** as the major product.

This procedure was attempted and was found to provide results exactly in accord with those reported. The only obvious disadvantage this procedure has is its employment of tin salts, which proved extremely difficult to remove and persisted even after column chromatography.

Nevertheless, with a relatively pure sample of **219** in hand, the Jones oxidation to **221a** was re-attempted, but disappointingly, gave largely the same results as before, suggesting that the contaminants present in the first instance were not actually responsible for the poor results. After considerable effort and re-examination of reaction conditions (lower temperatures, shorter reaction times and different work-up procedures were all attempted), a clean sample of **221a** was finally obtained, and the conversion to oxime ether attempted under standard conditions (equation 10).[137]

Equation 10



221a **221b**

produced in trace quantities

Sadly (considering the effort that had gone into trying to obtain **221a**) the crucial oxime was only produced in trace amounts, with NMR spectroscopy evidence again demonstrating the penchant for conjugated propargylic species to rearrange to the thermodynamically preferred allenes.

Due to this further setback, and the time expended trying to prepare **216** *via* Itsuno's method, at this point an alternative strategy into this key synthon was sought.

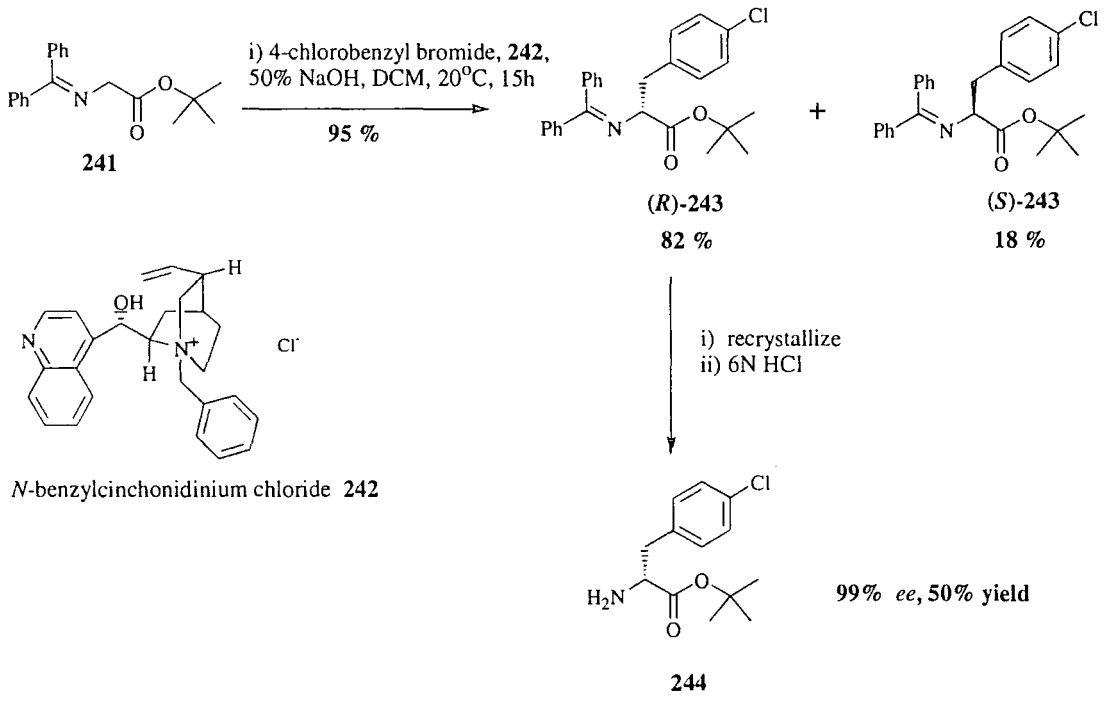
2.4.1.2 Strategy 2: Installation of the C-25 stereocentre by asymmetric phase transfer catalysis.

Phase transfer catalysis (PTC) plays an important role in organic synthesis.[138]
A thorough survey of the technique is beyond the scope of this discussion, but it suffices to say that as the technique grew in use since its emergence in 1965, much effort was directed towards development of an enantioselective variant, in which the use of chiral catalysts (commonly chiral quaternary ammonium salts, operating in exactly the same manner as their non-chiral counterparts) associate with the anion and carry it across the organic/aqueous interface, whereupon the anion reacts with the substrate. Tight interaction between the anion and the chiral catalyst generally allows reaction on only one face of the anion-catalyst complex, leading to non-racemic products.

Advances in asymmetric PTC have been made in several key areas of organic synthesis; among these, epoxidations,[139] Diels-Alder cycloadditions,[140] Darzens reactions,[141] Michael additions,[142] aldol condensations,[143] and α-hydroxylation of ketones[144] are notable as having provided some impressive results. Of particular interest for the purpose of this study were the examples of PTC involving enantioselective alkylation of carbon nucleophiles, an area in which many advances have been made through the pursuit of effective means to elicit the asymmetric synthesis of optically pure α-amino acids.[145, 146]

The first promising results in this area were disclosed by O'Donnell, who reported the racemic alkylation of prototypical glycine Schiff base esters such as **241**.[147] This was later followed by the first reported chiral phase transfer alkylation, which utilized a cinchona alkaloid (structures having stereogenic centres both at nitrogen, and on the carbon skeleton), affording α-amino acid **244** with excellent enantioselectivity following recrystallization and deprotection (scheme 49).[148]

Scheme 49



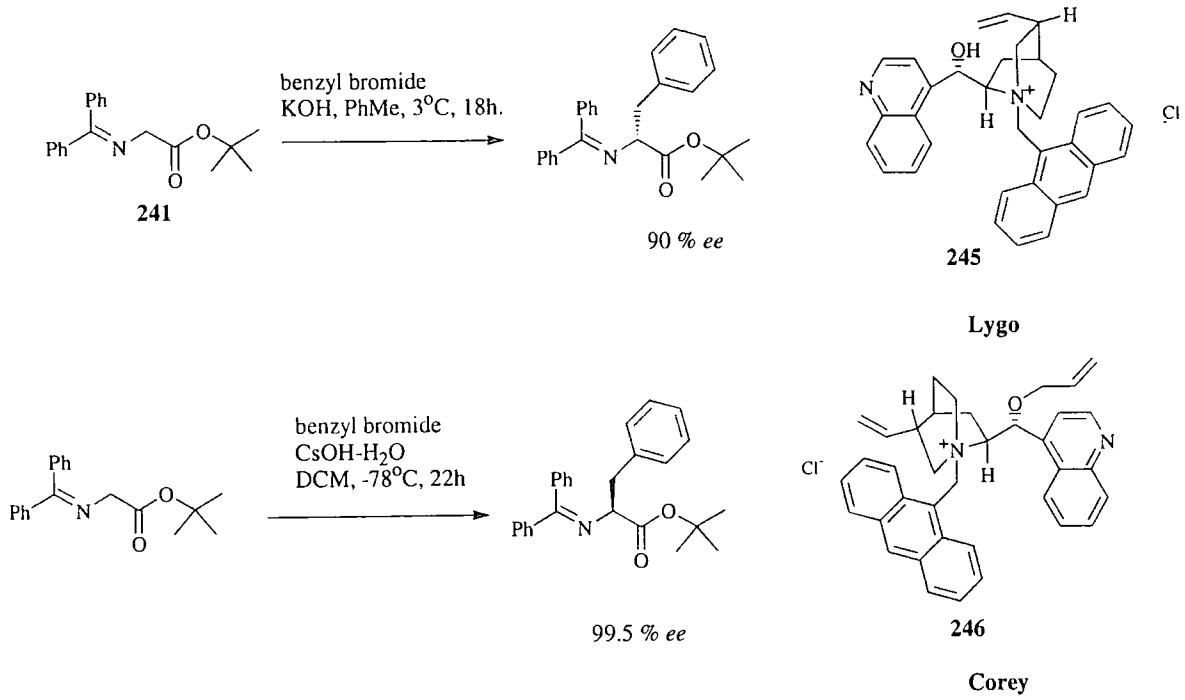
Throughout the following years, several improvements to the alkylation of such Schiff bases were made, including the development of a second generation of chiral catalysts (*N*, *O*-dialkylated salts of cinchona alkaloids) that gave higher initial selectivities in the case of **241** (up to 81% prior to recrystallization).[149] Then came a third generation of catalysts, independently developed by Lygo[150] and Corey.[151]

These *N*-9-anthracenylmethyl salts **245** and **246** mediated alkylation of Schiff base **241** with good to excellent *ee* (scheme 50), and from his work, Corey formulated a model to rationalize the stereochemical outcomes of these alkylation reactions.

In the Corey model, the positive charge on the quaternary nitrogen (which is delocalized onto the carbon and hydrogen atoms surrounding it in ammonium salts) interacts closely with the enolate oxygen of **241**, ensuring efficient transfer of stereochemical information (fig 20).

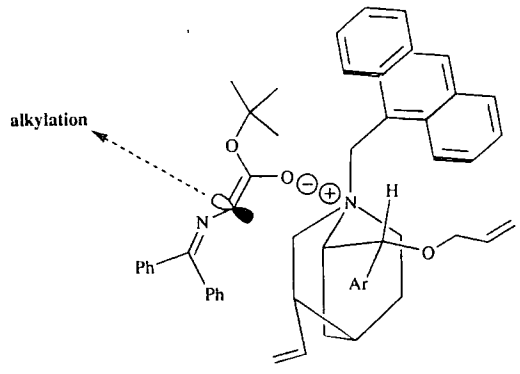
Other catalysts employed in asymmetric PTC include chiral metal-salen complexes,[152] TADDOL,[153] catalysis using NOBIN,[154] C_2-symmetric chiral quaternary ammonium salts,[155] and chiral derivatives of tartaric acid.[156]

Scheme 50

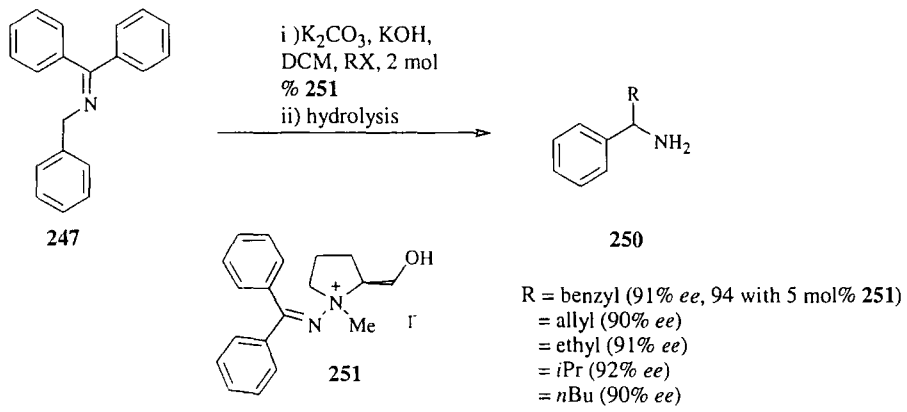


Considering the structure of the desired target (*S*)-**216**, one piece of work from the literature seemed propitious. Eddine and co-workers recently reported an example of imine α-alkylation under phase transfer condition, employing an amino alcohol derived hydrazonium salt **251** as chiral catalyst. Using a range of electrophiles, they were able to access amines **250** with good to excellent *ee*; yields were in the range 65-70% (scheme 51).[157]

Figure 20



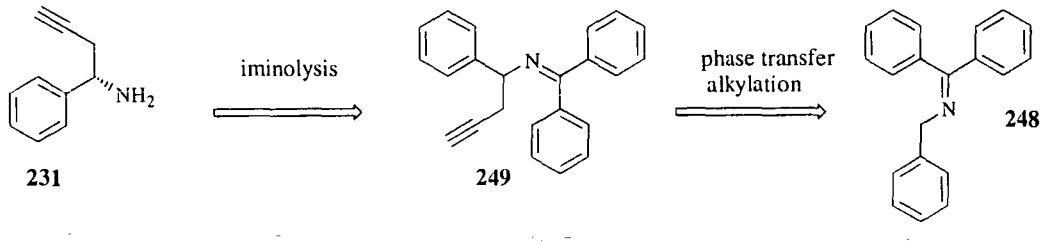
Scheme 51



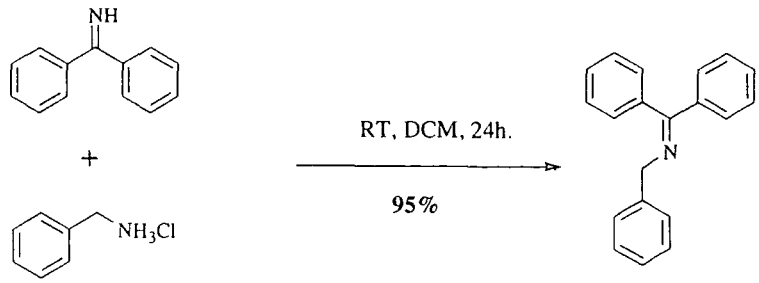
Although the authors had not attempted a propargylation, there was a singular documented early example from Favorskaya and co-workers of a propargyl electrophile used under phase transfer conditions to give racemic **231** from imine **247**, albeit in modest yield.[158] In light of this literature precedent, it was anticipated that **231** could be obtained *via* an asymmetric version of this procedure (figure 21), with the protected form (**221c**) then being elaborated as shown in figure 18.

With a view to first attempting a non-selective propargylation to test the method, and perhaps a subsequent trial hydroboration on the racemic amine (**221c→220d**), the preparation of **247** was achieved as shown in equation 11. Having obtained **247**, the phase transfer propargylation using propargyl bromide was undertaken; however, it should be noted that the experimental details given in the literature for this procedure (reference **157**) are inutile since the stochiometries are clearly incorrect. Nevertheless, the procedure was attempted with what was estimated to be more sensible ratios of reagents, and surprisingly it was found that the reaction returned a mixture of mostly starting material imine **247**, hydrolysis products propargyl alcohol (from hydrolysis of propargyl bromide) and benzophenone, plus a small quantity (<10 %) of the α-tautomer **248** (equation 12)

Figure 21

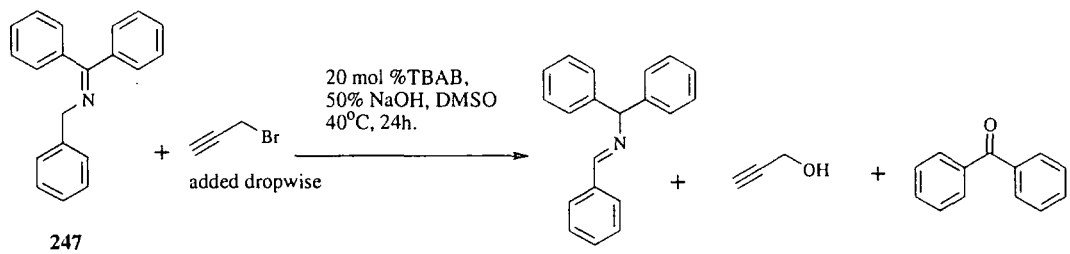


Equation 11



247

Equation 12

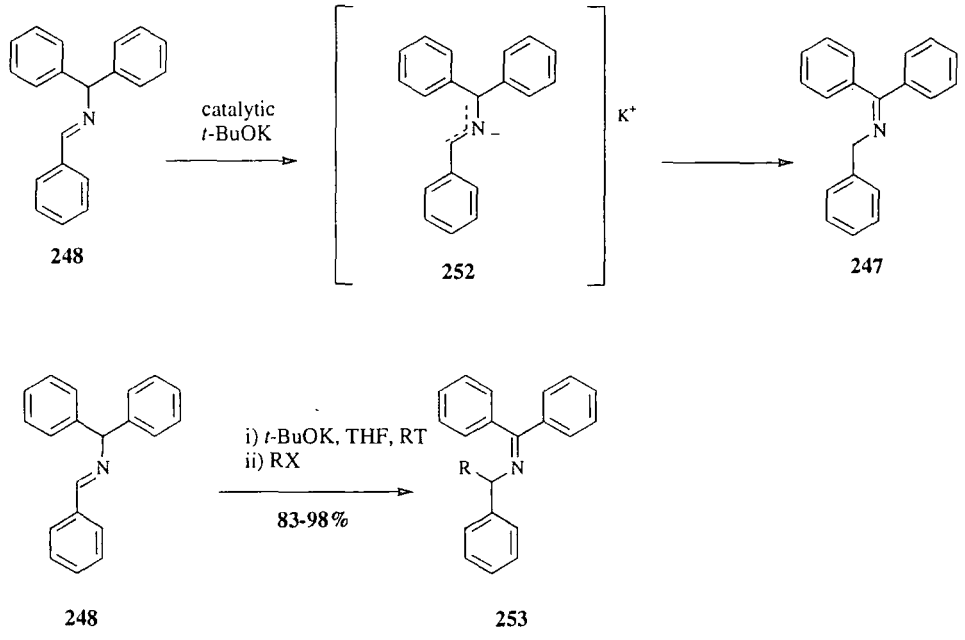


247 **248** + **247**

This result was duplicated exactly when the experiment was repeated. It was noted that when the reaction was performed, the mixture of the imine, salt and base gave rise to a deep violet colour, yet addition of a single drop of propargyl bromide to the reaction was sufficient to instantly neutralize this colouring, suggesting the colouring was due to a radical species present at low concentration. In order to probe the reaction, it was repeated on an NMR scale using d_6-DMSO, and although the spectrum indicated a slight downfield shift in the acetylene C≡C-H proton resonance from δ 3.60 to δ 3.67, there was no increase in complexity seen for the neighbouring methylene signal, suggesting the change was due to the formation of propargyl alcohol and not the propargylation of **247**. Somewhat puzzled by this outcome, information was sought from the literature concerning general alkylations of imines of this type, and produced an interesting finding that seemed to conflict with the results disclosed by Favorskaya.

Cainelli and Giacomini had reported that in the presence of base, imines such as **247** and **248** are in equilibrium, with the azaallyl anion **252** representing the intermediate species (scheme 52).[159]

Scheme 52

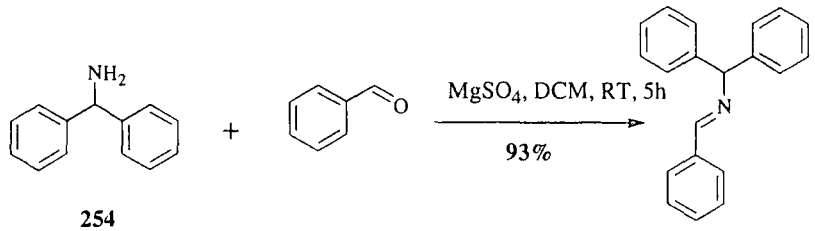


They had examined a range of *N*-diphenylmethanimine (**254**) derived imines and determined that in the presence *t*-BuOK, the acidic doubly benzylic proton was efficiently shuttled from the α-position in **248** to the α'-position in **247**, with the difference in pKa between the two positions driving the equilibrium. The best result was obtained with 1.2 equivalents of *t*-BuOK, giving a 60:40 ratio of **247** to **248** post work-up. Moreover, if the isomerization reaction was performed in the presence of an electrophile, concomitant irreversible alkylation was observed, effectively driving the reaction towards the formation of imines **253**, and affording *Z*-protected amines in excellent yields following iminolysis and *N*-protection.

The clear advantage of this method was that the lower pKa of imine **248** negated the use of harsh bases such as 50 % hydroxide, which seemed to effectuate largely hydrolysis of starting materials in the previous attempt to alkylate **247**.

Accordingly **248** was prepared as shown in equation **13**, and a tandem isomerization-alkylation procedure attempted as described above. However, when this was tried using 1.2 equivalents each of *t*-BuOK and propargyl bromide, a curious result was obtained. After work-up, the crude ^{1}H NMR spectrum showed a mixture of the desired propargylimine **249**, mostly a mixture of imines **247** and **248**, and also a compound whose identification was somewhat ambiguous from the NMR data.

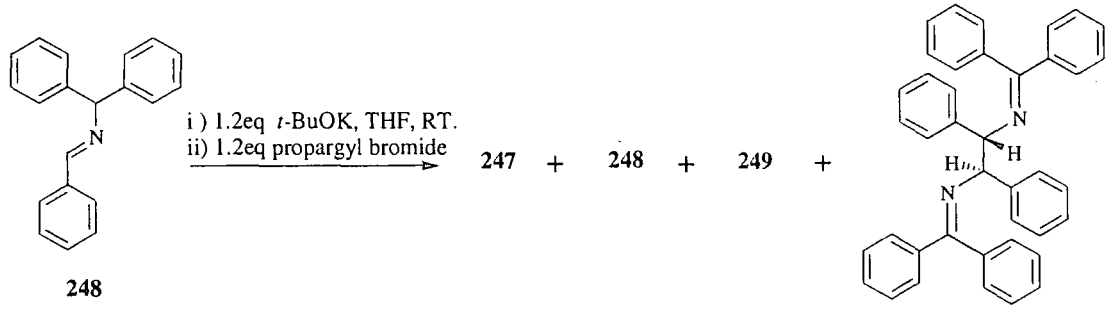
Equation 13



254 **248**

Purification of the reaction mixture was performed, and this unknown substance was isolated as a light brown crystalline solid that was subjected to XRD analysis. This brought prompt yet slightly surprising elucidation, and the result is shown in equation **14**, together with the crystal structure in figure 22.

Equation 14



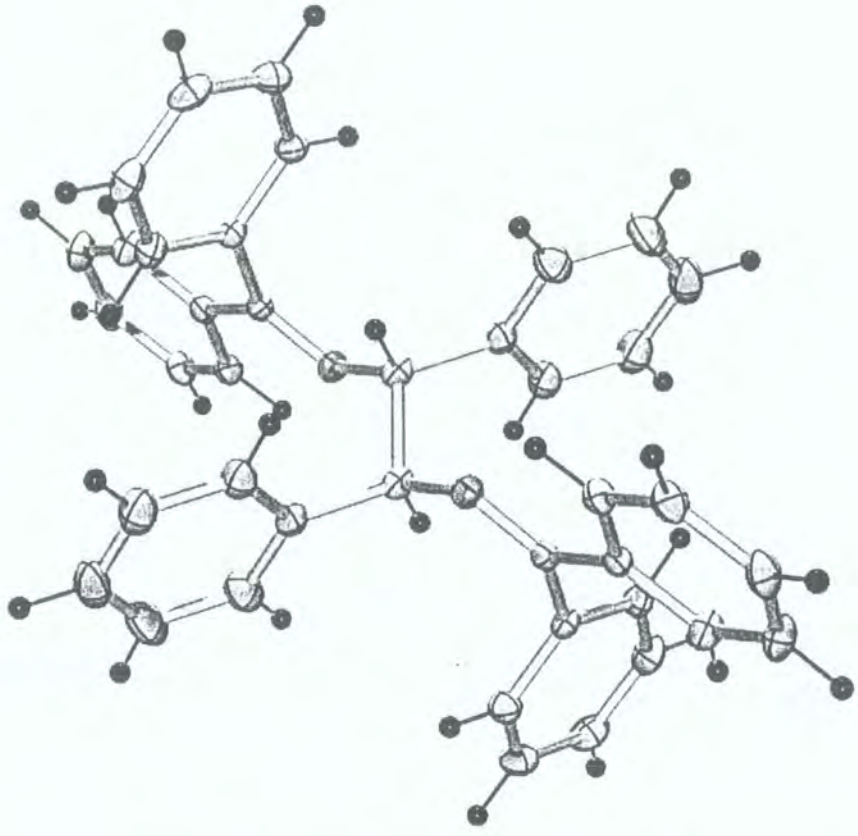
248 **255**

There are a few instances of **255** appearing in the literature,[160] but only one describes its preparation from **248** in a radical process involving elemental sodium![161] The supposition is that when using modest electrophiles like propargyl bromide, reprotonation of **252** is faster than alkylation, explaining both the low recovery of **249** and accounting for the presence of mostly starting material and tautomerized starting material after work-up. An explanation for the synthesis of **255** as a consequence of this process is not immediately obvious, since this compound would have presumably have been reported as a by-product of such tandem-alkylation procedures. However, a possible explanation is a radical dimerisation, requiring a suitable oxidant (possibly molecular oxygen) to generate a reactive intermediate from the anion initially generated by the action of base on **248**.

In order to improve the yield of **219**, a number of different conditions were tried, both varying the amount of *t*-BuOK (from 10 mol % to stoichiometric quantities) and electrophile (two equivalents and excess of propargyl bromide were tried), and also running the reaction at different temperatures. Unfortunately, none of these appeared to

have any significant bearing on the outcome of the reaction, and around this time in the project this method was discontinued as a more promising route to (*S*)-**216** emerged.

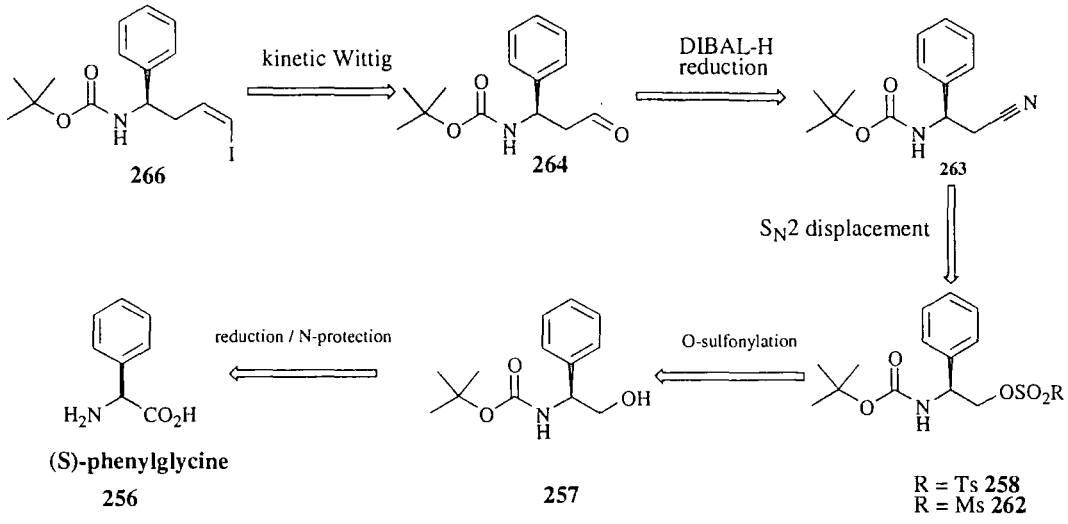
Figure 22: crystal structure of dimer **255**.



2.4.1.3 Strategy 3: Installation of the C-25 stereocentre using a chiral pool substrate.

As the decision to synthesize the diastereomer of viridenomycin having the (*S*) stereochemistry at C_{25} had been made based on what is perhaps a rather slight analogy to a related compound, it was felt that a strategy that allows ready access to either enantiomer of **216** might be prudent. With this in mind, it seemed that an obvious starting place would be a compound having the requisite stereochemistry already in place, and also one readily available in both enantiomeric forms. Considering the structure of **216**, a compound that fulfilled these requirements was the unnatural amino acid phenylglycine **256**, commercially available in both (*R*) and (*S*) forms. Thus, the approach to compound **216** that proved successful may be viewed as essentially a series of elaborations and homologations of phenylglycine; the retrosynthetic strategy, beginning with the *N*-carbamate protected form of (*S*)-**216**, compound **266** is shown in figure 22.

Figure 22

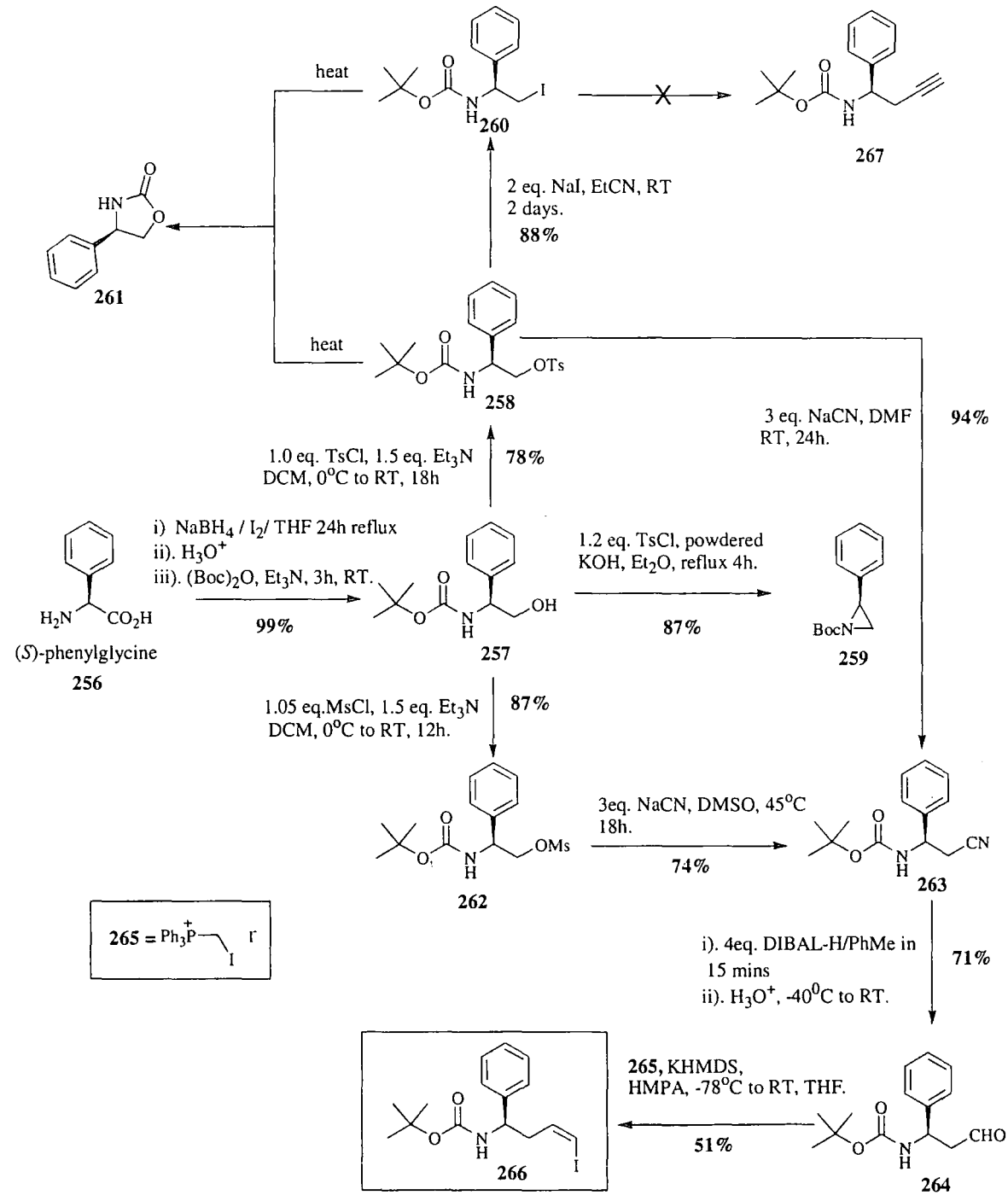


In the above approach, phenylglycine is reduced and protected as the *N*-Boc-amino alcohol **257**, before the hydroxyl function is converted to a suitable *O*-sulfonylate leaving group (it was imagined that nosyl, tosyl or perhaps mesyl would be suitable for this purpose). Having displaced the leaving group with cyanide to obtain β-amino nitrile **263**, a carefully controlled reduction with DIBAL-H to give aldehyde **264**, followed by a kinetic Wittig reaction (the Stork-Zhao modification mentioned in section **1.7**) should afford the requisite (*Z*)-iodide **266**. The full sequence of reactions and related side-reactions that were involved in the assembly of this iodide are shown in scheme 53. The first goal was to prepare **257**, the *N*-Boc amino alcohol. Although this is a commercially available compound, the high cost per gram meant that it was infeasible to purchase this reagent, since it was needed so early on in the synthesis. It has to be said that much of the chemistry shown in scheme **53** had to be developed, either by improving existing literature methods, which proved to be at best low yielding, and at worst, somewhat capricious; in other cases formulation of novel procedures was required.

Preliminary efforts towards compound **257** followed literature methodology, which advocates either a) *N*-protection of the commercial amino alcohol with di-*tert*-butyl dicarbonate (Boc anhydride) which is again expensive due to the high cost of the amino alcohol precursor[161] b) stepwise *N*-protection of the amino acid followed by reduction *via* the mixed anydride,[162] or c) a one-pot approach using LAH to first reduce the amino acid, followed by *N*-protection with Boc-anhydride.[163] However, a more current protocol that seemed advantageous was to first reduce the acid function, then

protect in a separate stage; using the aforementioned methods a-c, **257** was accessed in moderate yields, but the latter strategy offered the advantage of much higher yields, something that was deemed important given the early role of **257** in the synthesis.

Scheme 53



There are numerous methods available for the reduction of amino acids to chiral amino alcohols, a reflection of the importance of these compounds in organic synthesis.[164] In recent times, reductions based upon activated borohydride techniques

have become the vogue, offering many advantages over other methods, particularly with regards to safety when performing large scale reductions.

Especially popular is the method employing lithium borohydride and TMS chloride,[165] or the cognate procedure using iodine and sodium borohydride.[166]

Both these methods employ an oxidant to generate borane *in situ* and thus, the work-ups recommended are much the same as those suggested for an LAH reduction, where the use of strong hydroxide is necessary to break down the oxygen-metal complexes formed as a consequence of the reaction. Such extensive aqueous work-ups can lead to diminished yields, particularly considering the water-solubility of some amino alcohols, and it therefore seemed sensible to omit the work-up at this stage, instead choosing to perform a one-pot reduction-*N*-protection process, isolating **257** at the end of the sequence without the need to obtain the intermediate amino alcohol. Accordingly, following the reduction of (*S*)-phenylglycine **256** using the iodine-borohydride system, the reaction was cooled, quenched with methanol to destroy the excess borane, and then 1 equivalent each of triethylamine and Boc-anhydride was added to the cooled reaction. After stirring for 3 hours at ambient temperature, **257** was obtained in virtually quantitative yields following work-up and recrystallization.

It was in attempting the transformation of **257** to tosylate **258** that problems in the literature first emerged. Depending upon the temperature and base employed, adding *p*-toluenesulfonyl chloride (tosyl chloride) to a solution of **257** allows access to either the aziridine **259**, the oxazolidin-2-one **261**, or the tosylate **258**, which as scheme **53** illustrates, itself functions as an intermediate in the synthesis of both the other two, making **258** the most difficult to obtain with satisfactory yield and purity.

Although the mesylate **262** was not utilized until later on in the project, it is fitting to discuss early attempts at its preparation now, since many of the problems encountered during efforts to obtain tosylate **258** were also met in trying to synthesize this mesylate, most of these problems stemming from contradictory experimental details in the literature.

That both **258** and **262** show a great propensity to cyclize to the oxazolidin-2-one **261** even at ambient temperature is clear; testimony of this is found from two sources. First, from the literature methods, which report either tosylation or mesylation of **257** and subsequent cyclization of the *O*-sulfonylates as an expedient means to prepare these useful oxazolidin-2-ones. Treatment of **256** with tosyl chloride or methanesulfonyl chloride at 0 °C,[167] treatment of **256** with tosyl chloride and subsequent

heating to 60 °C[168] or use of excess *p*-toluenesulfonyl chloride at 25 °C[169] all provide oxazolidin-2-one **261** in yields varying from 70% to quantitative.

The second source was obtained from these studies; frequently, it was discovered that even if the temperature was kept low (-10 °C and below) and reaction times were kept to a minimum, significant amounts of **261** were present along with the desired *O*-sulfonylates. The problem was exacerbated at ambient temperature, where stirring 1 equivalent of tosyl chloride with **257** in DCM with either TEA or pyridine as base proved to be an easy route to obtaining oxazolidin-2-one **261** quantitatively!

It was found that the transformation **257**→**261** *via* *O*-sulfonylation generally showed little dependence on either the reactant stoichiometries or dilution, the base employed, or the solvent used. Reactions in DCM or mixtures of DCM-Et_2O, using bases such as pyridine, Hünig's base and TEA, changing the reactant stoichiometries (excess sulfonyl chloride, excess base), or using different reactant concentrations all had little effect on the overall outcome. It was observed that the formation of **261** was particularly rapid when the reaction was performed in DMSO, as anticipated.

It was also found that using 4-nitrobenzenesulfonyl chloride (in an attempt to prepare the nosylate derivative) was an even more efficient means of obtaining **261**, perhaps not surprising given the hardness of this sulfonylating reagent and the leaving group ability of *O*-nosyl. When using this reagent, it was noted that a threshold temperature at which the nosylate was formed and cyclization did not occur could not be found; lowering the reaction temperature to -18 °C effectively stopped the reaction completely, but warming it to -10 °C led to slow formation of the oxazolidin-2-one exclusively. In order to ascertain whether such a threshold temperature could indeed be found for the tosylation procedure, a series of NMR experiments were performed. These showed that 1 equivalent of TEA and 1 equivalent of tosyl chloride in *d*-chloroform slowly converted **257** to **258** with concurrent formation of **261** at 20 °C; both products were evident on the spectrum after 45 minutes. Lowering the temperature to 0 °C showed no conversion after this amount of time, and only after several hours were traces of both tosylate and oxazaborolidin-2-one seen. Conversely, addition of DMAP to either reaction led to accelerated formation of oxazaborolidin-2-one.

Indeed, the facile preparation of **261** has been reported from **257** using DMAP and Boc-anhydride alone at 20 °C,[170] and it was discovered from work in these laboratories that employing DMAP when attempting to generate **258** always led to cyclization, irrespective of the temperature, base, or solvent.

Given these observations and the conflicting accounts from the literature describing the syntheses of **261**, the majority of methods put forward for the preparation of the *O*-sulfonylates seem questionable.[171]

After considerable trial and error, the best conditions for the preparation of **258** were found to be treatment of **257** with 1.5 equivalents of tosyl chloride and 1.1 equivalents of TEA at 10 °C in DCM; after around 24 hours, although TLC indicated the reaction was not complete (**257** still remained), work-up after this time gave the tosylate in 70 % yield, after first removing the majority of the excess tosyl chloride by treatment with hot hexane (**257** and **258** are insoluble in hot hexane, tosyl chloride is not), then subjecting the remaining mixture to column chromatography.

Having obtained a reasonably satisfactory means of synthesizing **258**, attempts to transform it to iodide **260** were made, utilizing adapted literature methods.

Methods for the overall transformation of R-OH into R-I are few compared with the analagous transformations to R-Br or R-Cl; in most cases, R-OH must be activated as a suitable leaving group, either during the reaction, or *via* a suitable isolable intermediate. Activation by conversion to $-OSO_2R'$, Cl or Br, and subsequent displacement by I^- in halogen-exchange (or Finkelstein) type reactions[172] are commonplace, as are *in situ* activation methods employing reagents such as triphenylphosphine, iodine and imidazole.[173]

With a suitable leaving group in place, a number of literature procedures were attempted, involving treatment of solutions of **258** in acetone or 2-butanone with excess sodium iodide at either ambient temperature or under reflux.[174] Although these procedures gave satisfactory yields of **260**, total consumption of **257** was never seen, and heating in an attempt to push the reaction to completion induced cyclization to the oxazolidin-2-one **261**. Additionally, it has been found that 2-butanone, although superior as a solvent to acetone for this transformation, gave rise to a number of side-products that were never isolated and identified. These side products and the incomplete reactions necessitated time-consuming purification by column chromatography, and since using excess sodium iodide failed to improve the turnover, a number of alternative solvents were investigated. After a brief study, nitrile solvents were found to be superior to ketones or ethers (THF), and the one that proved most satisfactory was anhydrous propionitrile, affording pure **260** in 88% yield, without incidence of side reaction or cyclization to the oxazolidin-2-one.

At the same time these minor difficulties with the transformation **258→260** were being tackled, several means of preparing iodide **260** directly from **257** were assessed. The aforementioned method, employing triphenylphosphine, iodine and imidazole, is a valuable methods of converting alcohols into alkyl halides, but the notorious difficulty in removing the triphenylphosphine oxide by-product, which is often a time-consuming and yield-reducing endeavour and which is not always succesful anyway, can severely limit the utility of this reaction. An improvement to the procedure has been suggested.[161] In the method prescribed by Longobardo and co-workers, polystyryl diphenylphosphine is used instead of triphenylphosphine; this material gives comparable yields, yet allows the phosphine oxide by-product to be simply removed by filtration, affording the alkyl iodide as pure compound. This method was used to good effect, and **260** was obtained in 91% yield, however, there is sadly a serious drawback to this method, and it is not a synthetic consideration, but a financial one. The immoderate cost of polymer-bound triphenylphosphine (which puts a ~£60 per gram price on **260**) unfortunately precludes its use, even despite the tremendous advantages it offers.

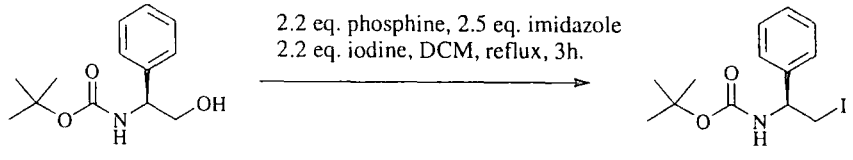
It is claimed that, in transformations that produce triphenylphosphine oxides as by-products (Mitsunobu reactions, Wittig reactions, or R-OH to R-X conversions using triphenylphosphine and CX_4 to name a few), the problem of removing the phosphine oxide can be alleviated through employment of tri-*n*-butyl phosphine instead, since tri-*n*-butyl phosphine oxide is ostensibly water-soluble and hence is removed during work-up .[175]

Intrigued and encouraged by this, a small-scale (0.21 mmol of **257**) study was undertaken to briefly investigate whether indeed there was any truth in this claim, and that using tri-*n*-butyl phosphine in place of triphenyl phosphine would make purification of **260** simpler by allowing the phosphine oxide to be simply washed out during the aqueous work-up.

For the sake of completion, a selection of other phosphines were incorporated into this study, and the results are displayed in table 10 (and see equation 15).
In this study, the reactions were performed in HPLC vials; although TLC was used to check for the appearance of **260** in the reaction, the disappearance of **257** could not be clearly observed by TLC since it coincided with the imidazole. For this reason, the reactions were heated at reflux for an arbitrary 3 hours, a time-period it was felt should be adequate to effect complete reaction given the phosphines employed.

Following this time, the presence of phosphine oxide in the ^{1}H NMR spectra of the crude products made conversion difficult to determine, so for this reason, only isolated yields are reported.

Equation 15



257 260

Table 10: relationship between yield and phosphine in the reaction shown in equation 15

Entry	Phosphine	Significant phosphine oxide present after aqueous work-up?	% Yield [a]
1	triphenylphosphine	yes.	67
2	polystyryl diphenylphosphine	no.	90
3	tri-*n*-butylphosphine	yes.	77
4	tris-furylphosphine	yes.	59
5	tri-*o*-tolylphosphine	yes.	70
6	tri-*t*-butylphosphine	- [b]	-
7	tri-*n*-octylphosphine	yes.	85
8	tri-cyclohexylphosphine	yes.	67

[a] isolated yield after column chromatography with gradient elution from neat pet. ether 60-80 to 6:1 pet. ether 60-80 / ethyl acetate; [b] no conversion to **260** was observed.

The first thing to note is that, at least in the case of the transformation of **257** into **260**, tri-*n*-butyl phosphine oxide is most definitely not removed during an aqueous work-up; indeed, the ^{1}H NMR spectra showed little difference between the amount present in the crude product prior to work-up, and that after work-up. Second, it was found that tri-*n*-octylphosphine was an excellent substitute for triphenylphosphine; in subsequent larger scale reactions, it was noted that this phosphine reacts rapidly and exothermically with iodine, and the overall reaction time is reduced to just under 1 hour. In addition, the long alkyl chains of the phosphine oxide by-product mean that it can be more easily removed using column chromatography, by eluting first with a higher boiling fraction of petroluem ether which drags the tri-*n*-octyl phosphine oxide through the column, yet fails to move **260**. Changing the solvent mix after all trace of phosphine oxide had been removed gives pure **260**. Apart from this time-consuming

practise, this method seems ideal; however, there is a disadvantage; the sheer molecular weight of tri-*n*-octylphosphine oxide and the fact that it is a greasy liquid and hence the bulk cannot be removed by recrystallization severely limits the scale this transformation can be performed on, as even small scale reactions produce relatively large quantities of this nusiance by-product. For this reason, tri-*n*-butylphosphine is perhaps the better alternative, although the claims made for it were found to be unsubstantiated; overall though, the procedure using the modified halogen-exchange was found to be superior, for reasons of experimental ease and consistency.

A recently disclosed method for the direct transformation of R-OH into R-I which uses a $CeCl_3.7H_2O$ / NaI system was also attempted, but this gave no reaction even after prolonged periods of time,[176] and attempts to transform **257** into the corresponding alkyl bromide using CBr_4 and PPh_3 led to **261** every time.[177]

The reason it was deemed desirable to obtain **260** was because it was imagined that the displacement of iodide by a suitable acetylene nucleophile should give easy access to **267**, allowing the route to **216** shown in figure **18** (in which **267** is simply **221b** where P=Boc) to be resumed. This proved not to be the case; attempts to react **260** with lithium acetylide-EDA complex (which continued to be a problem reagent), with TMS-acetylene and TBAF, and with the organocuprate generated from ethynylmagnesium bromide and copper iodide all failed to produce **267**, either giving rise to multiple products, or returning starting materials.

Continuing the theme of acetylidinations, the possibility of using aziridine **259** was suggested by a recent paper detailing the effective ring-opening of aziridines by trimethylsilyl compounds as a facile route to β-amino acids and 1,2-diamine derivatives.[178] Because of their high reactivity and capacity to function as carbon electrophiles, aziridine derivatives are useful synthetic intermediates and a number of ring-opening reactions on activated and unactivated aziridines have been reported.[179]

Hou showed that TBAF effectively triggers the reaction of nucleophiles TMS-X (X=N_3, CN, Cl) with a range of *N*-substituted aziridines, and this seemed encouraging. *N*-Boc aziridine **259** was thus prepared according to a literature method,[180] and subjected to a range of nucleophiles. Neither lithium acetylide nor TMS-acetylene / TBAF gave any indication of successfully ring-opening **259** to give **267**, and the only evidence of possible successful reaction was seen using an organocuprate, generated from ethynylmagnesium bromide and copper iodide; although ^{1}H NMR data showed the presence of a species having resonances at δ 2.3 (triplet with *J* 2.5 Hz) and δ 3.4 (double

doublet with *J* 6.8 and 2.5 Hz) which suggested **267**, all other means of analysis were inconclusive and further endeavours to obtain **267** were suspended.

During the course of investigations into literature methods for the transformation of *N*-Boc β-amino alcohols into *O*-sulfonylates, it had been noted that there was a reported procedure in the literature for the transformation of **257** to mesylate **258**, although no experimental details were given. Vaultier's group had reported the sequence **257** to aldehyde **264** *via* the mesylate **262**,[181] whereupon they then performed organometallic additions to this and other β-substituted *N*-Boc-β-amino aldehydes, providing a facile and novel route to enantiopure 1,3-disubstituted *N*-Boc-1,3-aminoalcohols.[182]

It was thought that elaboration of tosylate **258** (which was already in hand) in a similar manner should also enable access to aldehyde **264**, and then a kinetic Wittig reaction according to the method of Stork and Zhao[48] should provide the requisite iodide **266**. Accordingly, attempts were made to prepare the nitrile **263** *via* substitution reaction with sodium cyanide in DMF at ambient temperature over 24 hours, as described by Willis and Sutherland.[162]

The transformation **258**→**263** proved to be most capricious! Depite working perfectly the first time this procedure was undertaken, thereafter, numerous problems were encountered. The principal problem was one of incomplete reaction. Although the reaction completed with no trace of starting tosylate **268** after the prescribed time period the first time, every other time afterwards the reaction appeared to reach an equilibrium, returning a mixture of starting material and **263**. Heating the mixture to drive the reaction was out of the question given the predilection of **268** to cyclize, and slightly elevated reaction temperatures (up to 50 °C) made little difference.

The second serious issue encountered with this procedure was the the incidence of side-reactions; each time, the reaction would slowly change colour, taking on a red-orange hue, which proved to be a sure sign the reaction had failed. The successful reaction remains colourless throughout. TLC examination of a coloured reaction revealed a large number of components, including the starting material **268**, the nitrile **263**, and a number of other unidentified products. Time constraints meant there was little prospect for isolating these by-products in order to determine their origin and thus perhaps provide amelioration, so instead, a screen of various other solvents, cyanide sources and additives such as crown ethers was performed (table 11).

Table 11: factors affecting the transformation of 258 to 263.

Entry	Cyanide source	Solvent	Conditions / Additives	Result
1	1 eq NaCN	DMF	24h, RT.	poor conversion.
2	3 eq. NaCN	DMF	24h, RT	incomplete reaction, multiple products.
3	3 eq. NaCN	DMF	24h, RT, H_2O added.	incomplete reaction, multiple products
4	3 eq.NaCN	DMF	24h, RT, 5% diethylamine added	incomplete reaction, multiple products
5	3 eq. NaCN	DMF	24h, RT, 5% acetic acid added	incomplete reaction, multiple products
6	3eq.NaCN	DMF	24h, RT, 15-crown-5,	slow conversion after 24h, multiple products
7	3eq. NaCN	DMF	24h, RT ,15-crown-5, $MgSO_4$	slow conversion after 24h, multiple products
8	3 eq.KCN	DMF	24h, RT ,18-crown-6.	slower conversion than with NaCN, multiple products.
9	3eq. KCN	DMF	24h, RT	little conversion; product < 30%
10	3 eq. CuCN	DMF	24h, RT	no conversion seen after 24h.
11	3 eq. TBACN	DMF	24, RT.	poor conversion.
12	3 eq. NaCN	MeCN	24h, RT	poor conversion after 24h
13	1 eq. NaCN	IPA	24, RT	poor conversion, side products.
14	3 eq. NaCN	IPA	24, RT	poor conversion, side products.
15	1 eq. TBACN	IPA	24, RT	poor conversion, side products.
16	3eq. TBACN	IPA	24, RT	no conversion.
17	3 eq. NaCN	acetone	24, RT	no conversion
18	3 eq. TBACN.	acetone	24, RT	no conversion
19	3 eq. NaCN.	IPA / Et_2O	24, RT	no conversion
20	3 eq. NaCN.	IPA / DMF	24, RT	poor conversion

The reasoning behind entries 3, 4 & 5, where the reaction had been deliberately 'poisoned', came from the fact that the first time this reaction had been performed, a rather aging bottle of anhydrous DMF had been used. It is known that DMF slowly produces dimethylamine over time, and the supposition that trace amounts of base, acid or even water were having a detrimental effect on the reaction was thus tested by these entries. It was noted that entries 3, 4 & 5 all gave the 'dirtiest' reaction, giving rise to a red-orange solution and by far the most by-products on TLC. Other than demonstrating that other solvents, crown ethers and cyanide sources were either ineffectual or made no difference, the screen provided no elucidation as to why the transformation that had worked perfectly once never worked again. Magnesium sulphate was used in entry 7 to ascertain whether the presence of trace quantities of water were responsible; although care can be taken to exclude water during the reaction, and the solvent and **268** can be dried prior to use, drying large quantities of cyanide salts is a rather hazardous affair.

Given the problems with this method, the decision was made to attempt to access nitrile **263** *via* the mesylate **262**, but as mentioned previously, problems had been encountered in attempts to prepare **262** using literature methods. It should also be noted that the one time the transformation **258**→**263** had been successfully achieved, it had provided sufficient nitrile to attempt a large number of trial reductions using DIBAL-H and also Red-Al. All of these had failed, and as Vaultier's group had reported this reduction as part of a general sequence **257**→**264**, it seemed pertinent to contact him and request experimental details, since they were at the time unpublished.

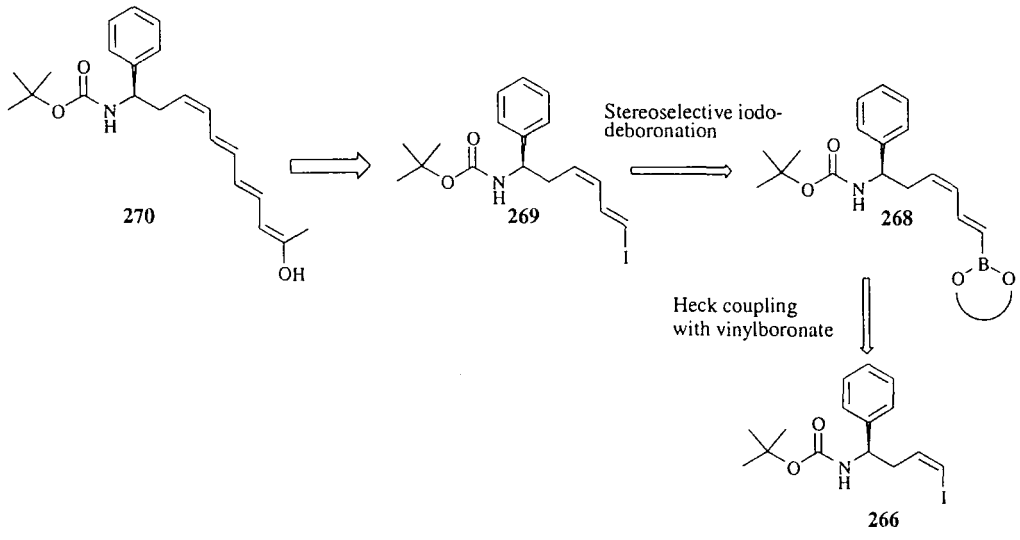
Having obtained experimental details and some salient general advice concerning the chemistry involved in the sequence **257** to **264**,[183] mesylate **262** and nitrile **263** were prepared in good yields. The Vaultier procedure recommends slow addition of 1 equivalent of mesyl chloride as a solution in DCM to a cooled solution of TEA and **257**, with the reaction then being allowed to stir at room temperature. In particular, the procedure also stresses the use of only freshly distilled mesyl chloride and TEA, and it was found that when this is done, the mesylate is formed almost quantitatively with no trace of oxazolidin-2-one **261**. This procedure was also adapted for the synthesis of **258**, where 1 equivalent of freshly recrystallized tosyl chloride (which was rendered acid-free by shaking a solution in Et_2O with 5 % NaOH) was added slowly as a solution in DCM to a cold solution of TEA and **257**; in exactly the same manner, pure **258** is isolated, and unlike before, the reaction goes to completion, without incidence of side-product formation. The likelihood is that the formation of these *O*-sulfonylates is highly acid sensitive, with protonation providing access to the

efficient leaving group R-SO_3H (R=Me or Tol) and hence encouraging cyclization to the oxazolidin-2-one.

Vaultier's procedure for the conversion of **263** to **264** utilizes a saturated solution of cyanide in DMSO; not a particularly pleasant mixture to handle, but nevertheless, one that proved to be effective. This reaction, performed at 45 °C over 18 hours, leads to **264** without incident, and again, applying this method to the transformation **258**→**263** proved successful; none of the aforementioned problems were encountered. Vaultier also provided conditions for the subsequent reduction of nitrile **263**, and considering the procedure disclosed, it is no small wonder previous attempts had failed! The procedure calls for exactly 4 equivalents of DIBAL-H to be added rapidly over just 15 minutes at -40 °C; the reaction is then cautiously quenched with MeOH before being allowed to warm to room temperature; the whole mixture is then poured into a separating funnel containing saturated ammonium chloride solution, and the resultant gelatinous precipitates are carefully broken down with progressively stronger HCl solutions. Unless this procedure is exactly followed, poor results are obtained, and unless the DIBAL-H is added as directed, no conversion is seen. The need to quench at low temperature is apparent, but the explanation for use of 4 equivalents of DIBAL-H and with such rapid delivery is elusive.

Having now obtained aldehyde **264**, the conversion to the (*Z*)-iodide by Wittig homologation with (iodomethyl)triphenylphosphonium iodide **265** was performed according to a procedure described in the literature,[184] and furnished **266** in moderate yield after chromatography. With this coupling partner finally in hand, the stage was set for a Heck reaction between **266** and a vinylboronate, which would provide dienylboronate **268**, and allow elaboration to the southern tetraene **270** as discussed previously (see figure 23 below, and figure 15, section **2.3.3**).

Figure 23



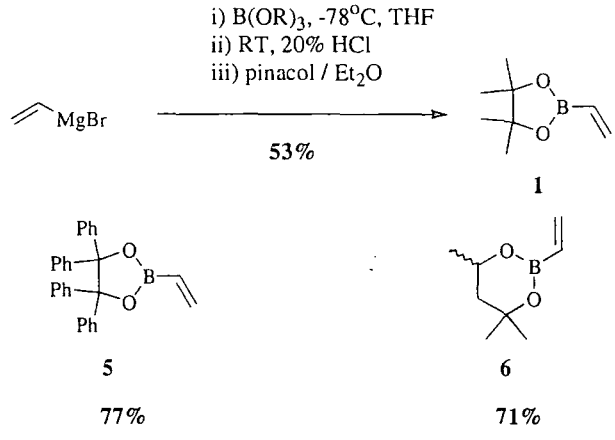
2.4.1.4 Vinylboronates and the methodology of sequential Heck coupling-iodo-deboronation: elaboration of 266

Before discussing the synthesis of **268**, it is pertinent to mention two related matters, concerning the preparation and use of boronates of general type **122**, and the manner in which such alkenyl boronates are able to provide access to alkenyl iodides with high stereoselectivity, this latter consideration being the crucial principle behind the project.

Vinylboronate **122** is readily prepared on multigram scale from commercial reagents by an adapted literature method.[185] In this procedure (outlined in scheme 53), trialkylborates are alkylated using a Grignard reagent, generating a tetrahedral borate. Use of triisopropyl borate instead of trimethyl borate confers a slight increase in yield due to the enhanced stability of this intermediate, but over the course of these studies this was found to be an insignificant advantage. Low-temperature quenching of this intermediate borate and subsequent transesterification with a diol affords the vinylboronate as an air- and moisture-stable product. In the case of **122**, this is a colourless liquid that can be distilled, but it is primarily this means of isolation that lowers the overall yield of **122**. The Grignard required for preparation of these vinylboronates is vinylmagnesium bromide, which is sold solely as a solution in THF. The problem is that THF and **122** azeotrope; in performing the distillation, one thus obtains THF, a constant boiling mixture of THF-**122**, and finally pure **122**, resulting in a loss of up to 30% of the total mass. Since vinylmagnesium bromide is only sold in THF solution, and since the prospect of making this Grignard reagent is unpalatable due to

the toxicity and difficulty of handling vinyl bromide, this situation unfortunately had to be tolerated. However, a couple of other minor issues with **122** gave reason to seek an alternative vinylboronate. Firstly, it was noted that occasionally (and particularly with very pure batches of **122**) the liquid would transform into a thixotropic material upon storage in the fridge; although a semi-liquid jelly-like consistency was most common, it was also observed that **122** would occasionally set almost solid. The obvious suggestion is polymerization, but aside from a brief examination of this material by ^{1}H NMR spectroscopy and mass spectrometry (which proved difficult since the material proved to be virtually insoluble in all solvents) which provided no real elucidation, the composition of this polymer and its mode of formation is unclear.

Scheme 54



The second issue concerns the volatility of **122**. It was noted that, when degassing Heck reactions by sparging with argon, it was possible to almost blow all the **122** out of the reaction (this was discovered accidentally, when 5g of **122** were reduced to about 1.5g in an attempt to degass the vinylboronate separately for the sake of convenience!).

In seeking an alternative to **122**, it was believed any diol that would give a hindered cyclic boronate woud be suitable, and accordingly, the vinylboronates from benzopinacol and racemic 2-methyl-2,4-pentanediol (hexylene glycol) were prepared as indicated in scheme **54**. Both showed the immediate advantage of increased yields compared to **122**; vinylboronate **271** is a grey solid and it thus easily obtained and purified by recrystallization, whilst **272** is a liquid, but fortunately one that can be easily distilled from THF solutions as a pure compound due to its much higher boiling point. Having obtained these new vinylboronates, a few trial couplings were attempted under classical Heck conditions *i.e.*, aryl iodides, with tri-*n*-butylamine as base, and palladium acetate / triphenylphosphine as the catalyst. By way of a comparison, a

number of couplings were undertaken with alkenyl bromides, since previous work had shown these to be more reluctant partners in Heck couplings with vinylboronate **122**.[98]

The results of these reactions are shown in scheme 55 and table 12.

Scheme 55

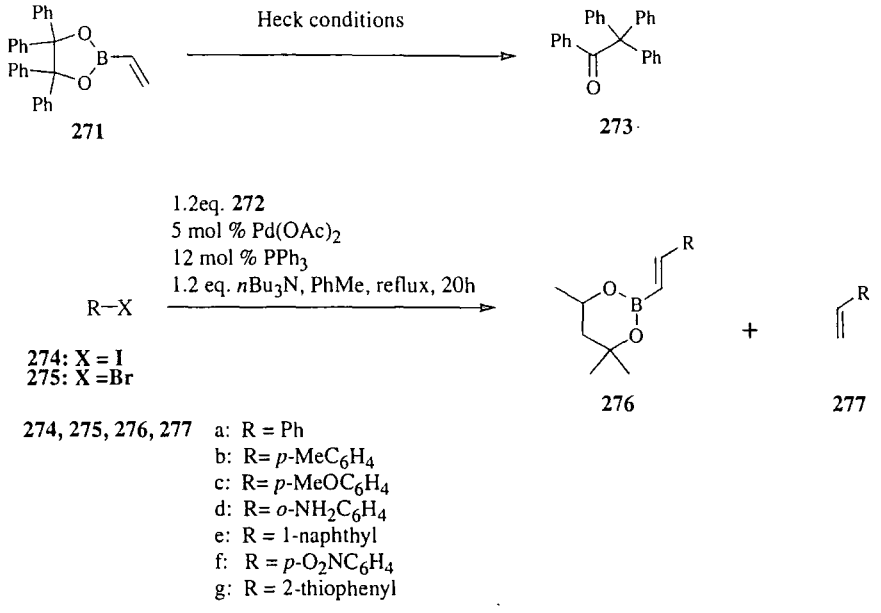


Table 12: Yields and Heck/Suzuki ratios in the reaction of vinylboronate 272 with various halides.

Entry	Halide	Conversion	276 : 277 ratio	Yield of 276
1	274a	100%(100%)	100:0(100:0)	97%(100%)
2	274b	100%(100%)	100:0(100:0)	77%(69%)
3	274c	100%(100%)	80:20(80:20)	48%(50%)
4	275b	>95%(64%)	80:20(80:20)	77%(51%)
5	275c	95%(>95%)	82:18(69:31)	40%(24%)
6	275d	40%(NA)	95:5(NA)	33%(NA)
7	275e	100%(100%)	65:35(62:38)	50%(57%)
8	275f	>90%(>90%)	85:15(87:13)	51%(48%)
9	275g	100%(0%)	100:0(-)	77%(0%)

reactions were performed in sealed tubes, using 5 mol % $Pd(OAc)_2$, 12 mol % PPh_3, 1.2 eq. vinylboronate **272** and 1.2 eq. *n*-Bu_3N; PhMe reflux for 8h (4 days for **275**). Figures in brackets are previous results obtained using vinylboronate **122**. NA denotes no data exists for comparison.

The first thing to note is that under Heck conditions, vinylboronate **271** gives only the pinacol reaction product ketone **273**; this was perhaps to be expected, given the migratory aptitude of -Ph in this rearrangement.

Inspection of the results in table **12** reveals what may be considered normal Heck reactivity profiles, with the order of reactivity between iodides **274** and bromide

275 roughly in accord with that normally observed and indicative of a mechanism involving a rate-determining oxidative addition of Pd(0) to R-X.[187]

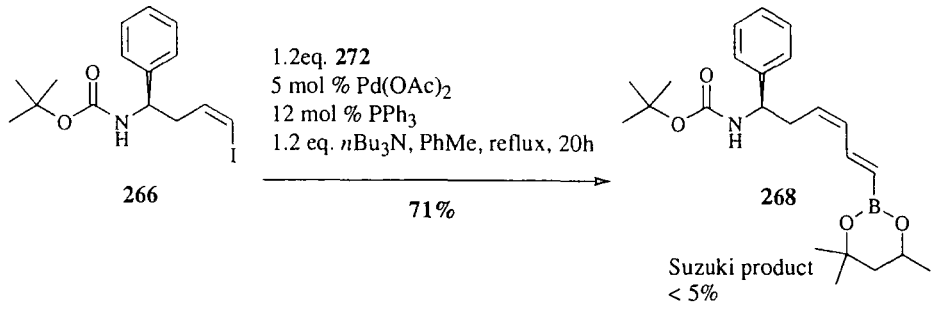
Although at first glance the data suggest **272** is an improvement over **122**, it has to be said that some of the comparisons are invalid because the conditions employed previously were markedly different to the ones used here; for instance, in entry 5, the conditions that provided **276c** were much milder (reflux in MeCN for 24h). The only signficant improvement is in the coupling of 2-Bromothiophene; previously, it had been found that 2-Iodothiophene afforded the Heck product in 46% yield (92:8 Heck/Suzuki) and then only if AgOAc was added; reaction without this additive gave poor (<5%) conversion to the Suzuki product exclusively. 2-Bromothiophene had never been successfully coupled, but again, it must be said that the comparison is slight since such forcing conditions as used here were never tried in the previous study.

Since **272** seemed comparable in terms of reactivity, and superior in terms of preparation, it was adopted as a replacement for **122** for the remainder of the project. The first successful deployment of it in a Heck coupling reaction of direct relevance to ths synthesis at hand was in its coupling with **266**. It has been said that there are almost as many different conditions employed in the Heck reaction as there are examples of its use, and in the absence of an exemplary literature procedure, finding successful reactions conditions for a given transformation can amount to little more than trial and error, even in light of recent suggestions gleaned from mechanistic studies and a wealth of experimental data.[186b]

A good place to start is often with traditional Heck conditions (those employed in the study described in table 12), and fortuitously, such conditions turned out to be ideal in preparing **268**. As illustrated by equation **16**, **268** was obtained in good yield following chromatographic purification, with only an accompanying trace (<5%) of the Suzuki product.

With this key dienylboronate in hand, efforts were directed towards its elaboration to the southern tetraene, which commenced with attempts to obtain dienyl iodide **269** *via* stereoselective iodo-deboronation of **268**.

Equation 16



As was mentioned in the introduction, an efficient protocol enabling the preparation of (*E*)- or (*Z*)-iodides *via* boronates such as **268** has been developed (see scheme **21**). This protocol builds upon Brown's methodology, where it was discovered that the geometery of the iodides produced was solely dependent upon the order of addition of reagents.[76] In the original study, sodium hydroxide and iodine were used to elicit iodo-deboronation; as a consequence of later work in these laboratories, it was found that a more electropositive source of iodine was needed when dealing with bulky pinacol esters (the original study has examined vinylboronic acids[187] and their diisopropyl esters),[188] and iodine monochloride proved to be ideal.[77]

A mechanism explaining the stereoselectivity of the iodo-deboronation process is presented in scheme 56.

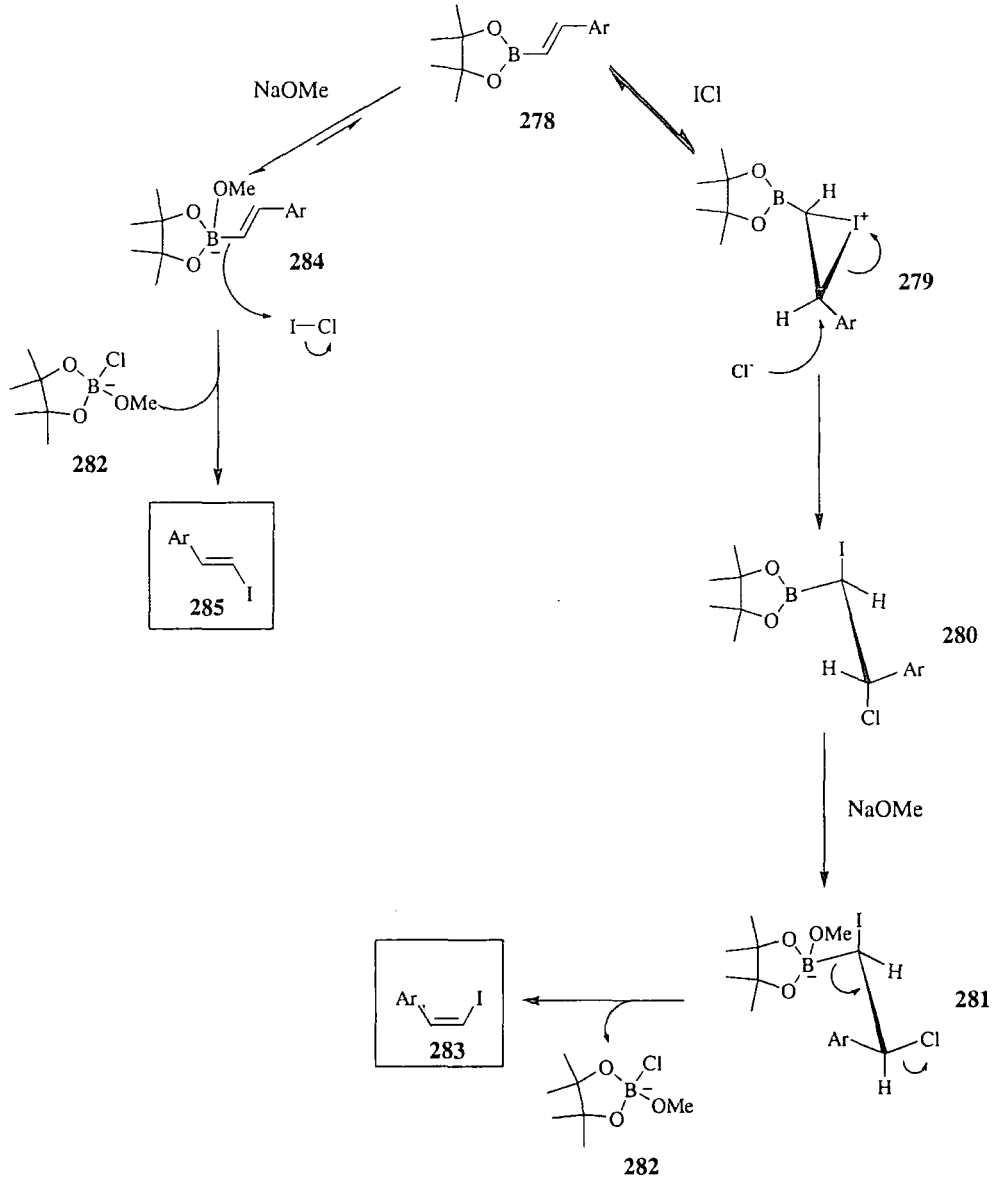
Reaction of styryl boronates **278** with ICl leads to the dihalo adduct **280**, presumably *via* the intermediate cyclic iodonium ion **279**. Addition of MeO^- to this species generates the "ate" complex **281**, which leads to rapid *anti* elimination of **282** and inversion of stereochemistry, producing (*Z*)-styryl iodides **283**.

Conversely, pre-complexing **278** with MeO^- generates the "ate" complex **284**, which undergoes direct iodination by the I^+ source with retention of stereochemistry, affording the (*E*)-styryl iodides **285**.

Unfortunately, when this iodo-deboronation sequence was applied to **268**, adding first sodium methoxide at -78°C, then ICl as a solution in DCM, extensive decomposition was observed, evident from both the TLC of the reaction, and from the crude ^1H NMR of the reaction mixture, which suggested (among other unexplained phenomena) what appeared to be partial cleavage of the *N*-protecting group (this was deduced by a resonance at δ 1.5, indicative of *t*-Bu group due to S_N1 Boc fragmentation).

Suspecting this to be perhaps down to the use of sodium methoxide, the reaction was repeated and the TLC taken prior to addition of ICl; however, this did not appear to indicate that methoxide alone had caused the decomposition of **268**, and so it was

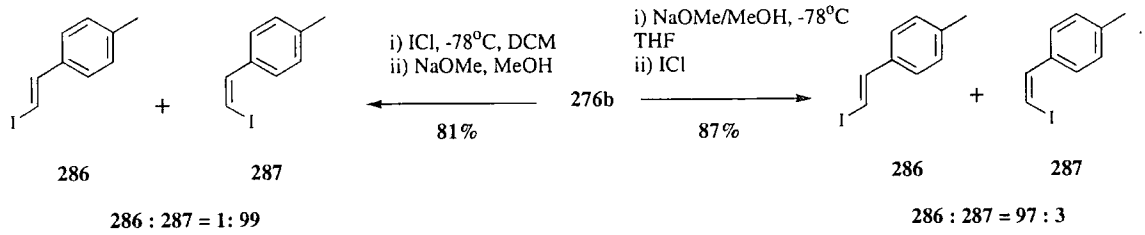
Scheme 56



assumed that perhaps **268** was simply intolerant to the conditions necessary to effect iodo-deboronation; in particular, the functional group intolerance of iodine monochloride was mooted as being a possible cause of the problem. An alternative was briefly investigated; during the course of these studies a reagent came to light that was purportedly a potentially useful alternative to ICl, being somewhat more stable and easier to handle. This reagent, pyridine-ICl complex,[189] is simply obtained by stirring a cold solution of ICl in DCM with 1 equivalent of pyridine, and the resulting complex is then precipitated by the addition of hexane, and then isolated as a yellow powder after

filtration and drying. Although certainly easier to handle, it proved to be a very weak source of I^+; too weak in fact to be of any utility in this synthesis. In a trial reaction, iodo-deboronation of **276b** by ICl gave results exactly comparable to those previously disclosed,[see ref. 98, compounds 73 &74] both in terms of yield and selectivity (scheme 57).

Scheme 57



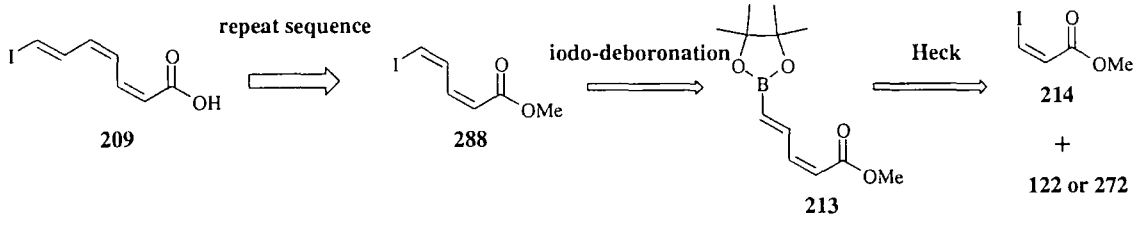
However, when pyridine-ICl complex was substituted for ICl, iodo-deboronation was found to proceed very sluggishly indeed, with only around 10% conversion to iodides **286** and **287** being seen. Performing the reaction at ambient temperature led to a marginal increase in yield, but still this complex is seemingly a very weak source of I^+ compared alongside ICl itself, and current research being carried out in the group bears testimony to this.

2.4.2 Routes into the northern hemisphere triene 209.

Tackling fragment **209** proved to be the major stumbling block of the project, solely due to the problem of an unexpected side-reaction encountered right at the start of the planned synthesis towards **209**, a problem that ultimately proved to be an intractability too difficult to circumvent.

Before discussing this side-reaction, a review of the planned procedure to assemble **209** is fitting. As was first shown in figure 14, **209** was to have been assembled *via* a Heck coupling between known iodoacrylate **214** and a vinylboronate, to give a dienylboronate **213** that would then be subjected to iodo-deboronation with inversion, producing (*Z*, *Z*)-dienylester **288**. A second coupling of this diene with vinylboronate, and subsequent iodo-deboronation with retention of olefin geometry was to provide triene **209** after deprotecting the ester to unmask the carboxylic acid group need for the attachment of **209** to the southern tetraene **210**.

Figure 24



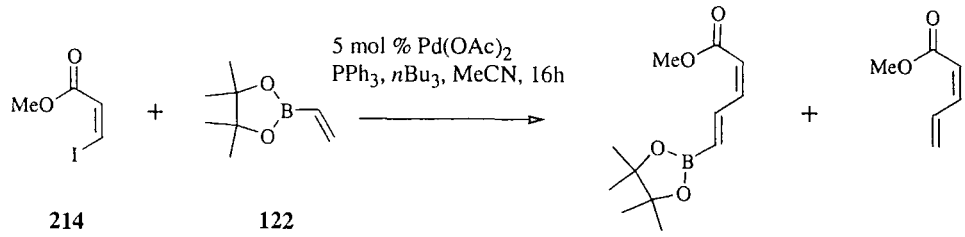
Regrettably, the synthesis described here did not get as far as **213**, for reasons that will now be elaborated on.

2.4.2.1 An unexpected and problematic result.

Having prepared iodoacrylate **214** according to a literature procedure by treatment of methyl propiolate with sodium iodide in glacial acetic acid,[190] attempts were made to couple it with vinylboronate **122**.

Once again, it was elected to first try a coupling under rather traditional Heck conditions, using palladium acetate, triphenylphosphine, and tri-*n*-butylamine as base. The expected outcome of this is shown below in equation 17 below, where it was anticipated at worst a mixture of Heck and Suzuki products would be obtained.

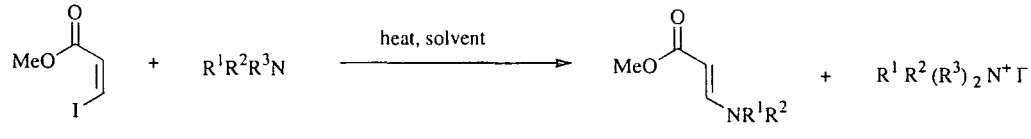
Equation 17



214 **122** **Heck product** **Suzuki product**

Instead, following work-up, a new compound was isolated whose ^{1}H NMR spectra possessed unexpected doublets having *J* 13.2Hz at δ 4.50 and 7.41 (compared with doublets at δ 7.55 and 6.91 with *J* 9Hz for acrylate **214**), together with signals which showed the presence of only two *n*-butyl groups. This was tentatively assigned as methyl (*E*)-dibutylaminoacrylate **290b**, which may have arisen from a Michael addition-elimination sequence of tributylamine on iodoacrylate **214**, followed by loss of a butyl group. In order to confirm this series of events, further experiments were performed between both secondary and tertiary amines **289** and iodoacrylate **214**.

Scheme 58



214 **289** **290** **291**

289

a: $R^1=R^2=R^3=Et$
b: $R^1=R^2=R^3=n$Bu
c: $R^1=Et$, $R^2=R^3=i$Pr
d: $R^1=R^2=-(CH_2)_4-$, $R^3=Me$
e: $R^1=R^2=-(CH_2CH_2)_2O-$, $R^3=Me$
f: $R^1=R^2=Et$, $R^3=H$
g: $R^1=R^2=i$Pr, $R^3=H$
h: $R^1=R^2=-(CH_2)_4-$, $R^3=H$
i: $R^1=R^2=-(CH_2CH_2)_2O-$, $R^3=H$.
j: $R^1=R^2=Bn$, $R^3=H$.
k: $R^1=R^2=-(CH_2)_5-$, $R^3=H$
l: $R^1=R^2=-(CH_2)_5-$, $R^3=Me$

amino acrylate 290

a: $R_1=R_2=Et$
b: $R_1=R_2=n$Bu
c: $R_1=Et$, $R_2=$iPr
d: $R_1=R_2=-(CH_2)_4-$
e: $R_1=R_2=-(CH_2CH_2)O-$
f: $R_1=R_2=Bn$
g: $R_1=R_2=Bn$
h: $R_1=R_2=-(CH_2)_5-$

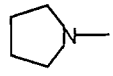
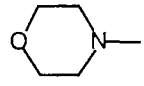
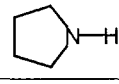
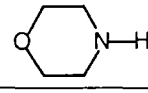
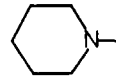
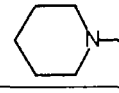
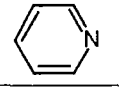
salt 291

a: $R^1=R^2=R^3=Et$
b: R1=R2=R3=*n*Bu
c: $R^1=Et$, $R^2=R^3=i$Pr
d: $R^1=R^2=-(CH_2)_4-$, $R^3=Me$
e: $R^1=R^2=-(CH_2CH_2)_2O-$, $R^3=Me$
f: $R^1=R^2=Et$, $R^3=H$
g: $R^1=R^2=i$Pr, $R^3=H$
h: $R^1=R^2=-(CH_2)_4-$, $R^3=H$
i: $R^1=R^2=-(CH_2CH_2)_2O-$, $R^3=H$.
j: $R^1=R^2=Bn$, $R^3=H$.
k: $R^1=R^2=-(CH_2)_5-$, $R^3=H$
l: $R^1=R^2=-(CH_2)_5-$, $R^3=Me$

The results of this study are shown in scheme 58, and the yields are given in table 13. Amino acrylates **290** were typically obtained in near quantitative yields in acetonitrile using 2 equivalents of base, after isolation from the 1:1 mixture with the ammonium salt

291. The reaction was preferably carried out in toluene, since in most cases this allowed simple separation of the salt **291** (by filtration) from the amino acrylate **290**.

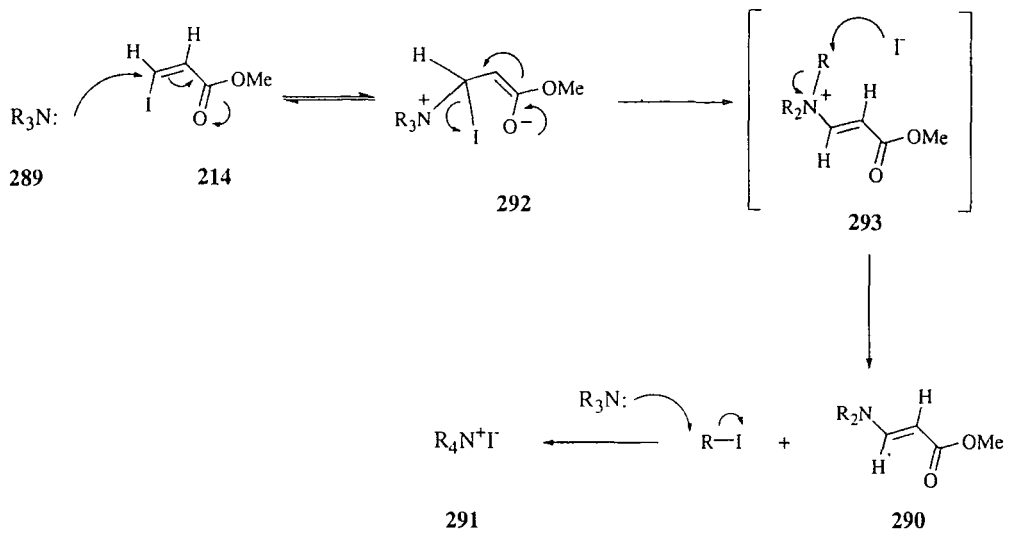
Table 13: yields in the reaction of amines 289 with iodoacrylate 214.

Entry	Amine **289**	**290** (Yield / %) in PhMe	A **291** (Yield / %) in PhMe	**290** (Yield / %) in MeCN	**291** (Yield / %) in MeCN
1	Et_3N	**a** (96)	**a** (86)	**a** (95)	**a** (77)
2	$^nBu_3N$	**b** (94)	**b** (96)	**b** (94)	**b** (79)
3	$^iPr_2NEt$	**c** (93)	**c** (96)[b]	**c** (91)	**c** (70)[b]
4		see a	see a	**d** (92)	**d** (74)[b]
5		see a	see a	**e** (94)	**e** (86)
6	Et_2NH	**a** (92)	**f** (88)	**a** (93)	**f** (83)
7	$^iPr_2NH$	**f** (94)	**g** (96)	**f** (90)	**g** (77)
8		**d** (93)	**h** (94)	**d** (91)	**h** (72)
9		**e** (92)	**i** (94)	**e** (93)	**I** (72)
10	Bn_2NH	**g** (94)	**j** (94)	**g** (95)	**j** (90)
11		**h** (91)	**k** (92)	**h** (93)	**k** (91)
12		see a	see a	**h** (94)	**l** (88)
13		0[c]	0[c]	0[c]	0[c]
14	Et_2NPh	0[d]	0[d]	0[d]	0[d]

[a]obtained the corresponding methyl *cis*-ammoniumpropenoate iodide **293** quantitatively. [b]Salt not isolated; yield was estimated from ^1H NMR of crude reaction. [c]Complex mixture of products results. [d]No reaction observed.

Assignment of the (*E*)-alkene geometry of the products was unambiguous by ^1H NMR data; all of the amino acrylates exhibited a pair of doublets with coupling constants in the range 13.1-13.5 Hz. Additionally, analytical data was in full agreement with that reported in the literature for those amino acrylates that had been previously synthesized.[191] Our mechanistic rationale for the formation of these adducts is outlined in scheme 59, and involves a reversible addition of the amine **289** to the acrylate **214** forming an intermediate ammonium propenolate zwitterion **292**, analogous to the first step in the Baylis-Hillman reaction.[192] This zwitterion would rapidly lose iodide to form a methyl 1-ammoniumpropenoate iodide **293**.

Scheme 59



In both acetonitrile and toluene, subsequent reaction of iodide ion on salt **293** accomplishes dealkylation, giving rise to an alkyl iodide, which in turn reacts with the second equivalent of amine **289** yielding the salt **291** in almost all cases (see Table 13). The exceptions to this are Entries 4, 5 and 12 (Table 13), where *N*-methylated cyclic tertiary amines are employed. For these cases, in acetonitrile, dealkylation occurs as for other amines, however in toluene, the methyl 1-ammoniumpropenoate iodide salt **293** rapidly precipitates before dealkylation can occur allowing its isolation. In addition, it is interesting that loss of *i*-Pr over occurs in preference to loss of Et when using Hünig's base (Entry 3, Table 13), which suggests that in this case an S_N1 reaction is involved in the iodide-mediated dealkylation process. In contrast, the less nucleophilic base, diethylaniline, did not react under the reaction conditions employed, whereas pyridine did react resulting in a complex mixture of products.

Reported uses for amino acrylates are quite scarce; there are a few examples of them being utilized in natural product chemistry, but in each case they have been prepared through reaction of a secondary amine with a propiolate ester. There are also reports detailing the preparation of *trans*-ammonium halides like **293** as stable compounds and there subsequent use as Diels-Alder dienophiles.[193] These salts are usually prepared by reaction of a quaternary ammonium chloride or bromide with a propiolate ester under slightly milder conditions and in these cases there were no reports of amino acrylate formation, suggesting that elimination of iodide leading to amino acrylate formation is a facile process compared with loss of chloride or bromide.[194]

Whilst the discovery of this side-reaction was an interesting development,[195] it represented a significant problem for the planned synthesis of the northern triene; not

being able to use any of the commonly employed amine bases in a Heck reaction due to their reaction with the starting material is a severe limitation!

Indeed, the above study had served not only to explore the scope of the Michael addition-elimination sequence, it had also illuminated which bases were unusable, and thus which amine bases remained that could potentially still be used. This left a limited number of possibilities if it was still wished to pursue this line of approach towards **213**, but first, realizing that the root cause of the problem was the capacity of **214** to act as a Michael acceptor, the idea of using an alternative alkenyl halide at the same oxidation level, yet that was not a Michael acceptor was proposed. It would probably have been possible to reduce **214** to the iodoalcohol, perform the Heck coupling, and then re-oxidize back up to the acid oxidation level at a later stage, but this was deemed inadvisable given the presumed sensitivity of the nascent polyene chain as the northern triene was elaborated, so the decision was made to remain at the acid oxidation level, which called for an acid protecting group.

2.4.2.2 Explorations of orthoester chemistry to circumvent this problem.

Suitable protecting groups that have found increasing utility in organic synthesis are the orthoesters; either the 2,6,7-trioxabicyclo[2.2.2] octane ring system (the so-called OBO esters) of Corey,[196] or the more recent 2,7,8-trioxabicyclo[3.2.1] octanes (ABO-esters) of Wipf.[197] The advantage of such protecting groups (the assembly of which is exemplified in scheme 60) is that they are one of few carboxylic acid protecting groups that are resistant to nucleophiles and bases, the acidic hydroxyl group is removed as too is the electrophilic carbonyl function, greatly increasing the pKa of the α-hydrogens. Additionally, the facility of their preparation, from the oxetanyl esters **294** with BF_3-etherate in the case of the OBO-esters **295**, and from the zirconocene catalyzed rearrangement of epoxy esters **296** in the case of ABO-esters **297**, makes them particularly appealing as protecting groups.

First to be examined were the OBO-esters, and the retrosynthetic route to the protected form of **209**, OBO-triene **298** is shown in figure 25.

Scheme 60

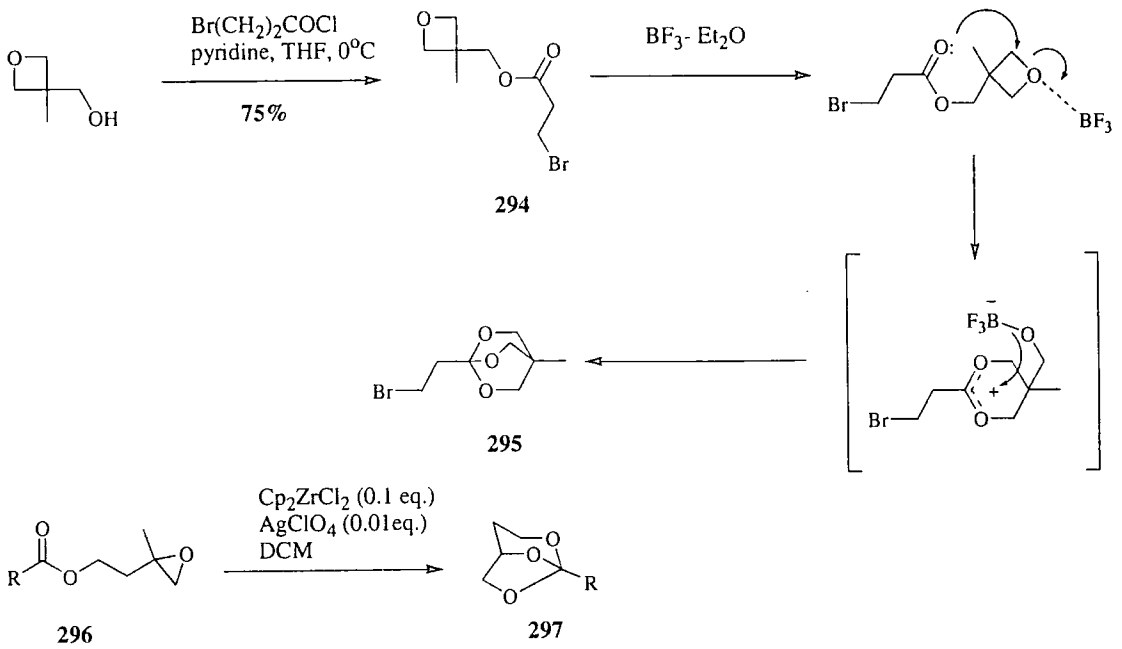
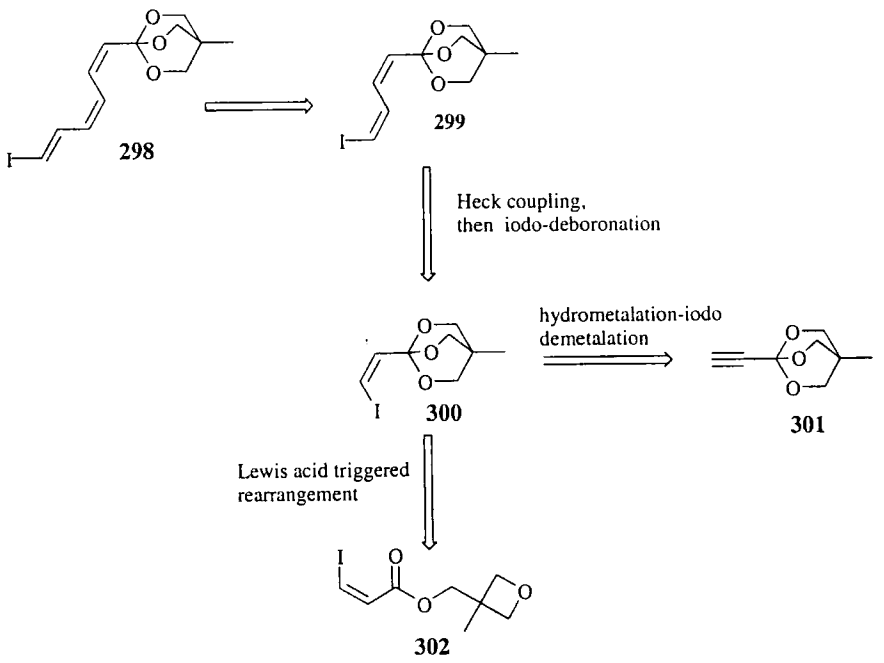


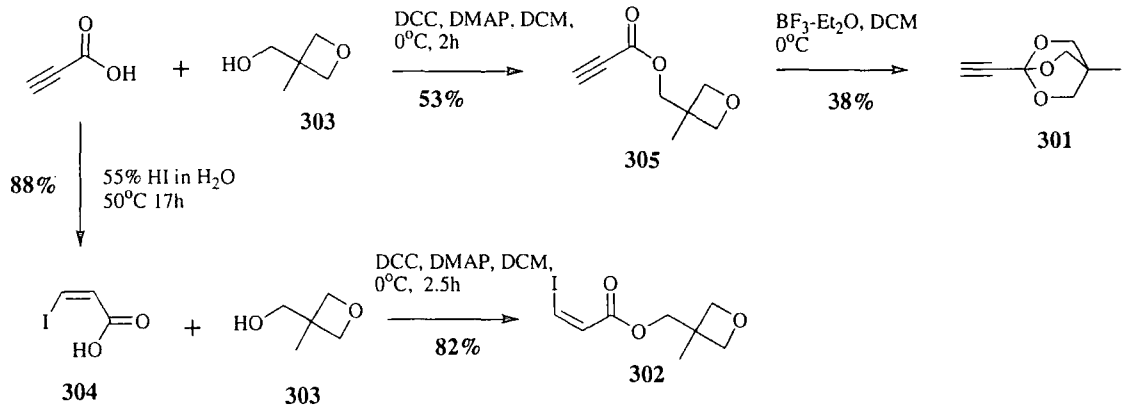
Figure 25. Retrosynthesis of the OBO ester **298**.



In this strategy, it was envisaged that **300** would function as the non-Michael acceptor replacement for **214**, with the elaboration to **298** occurring exactly as planned before. Two approaches were conceived to reach **300**; a hydrometalation / stereoselective iodo-demetalation procedure on acetylenic ortho-ester **301** to install the requisite (*Z*)-alkenyl iodide functionality, or by triggering the rearrangement on the

approriate iodo-oxetanyl ester **302**. Accordingly, **301** and **302** were prepared as shown in scheme 61.

Scheme 61



The rearrangment of **305** to **301** proved difficult; although **301** is a literature compound, the rearrangement failed every time under the prescribed conditions;[198] instead, it was found that the conditions described by Corey for the rearrangement of similar oxetanyl esters were more suitable, and gave **301** as a white waxy solid that could be recrystallized from hexane (see figure 26), but the yields were consistently poor. Due to these low yields, efforts were focussed instead on oxetanyl ester **302**.

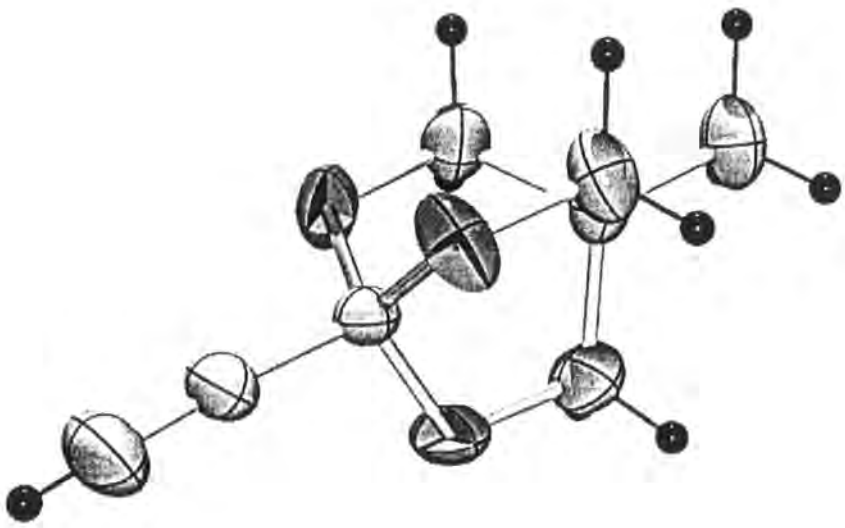
Commencing with the stereospecific hydroiodination of commercial propiolic acid to provide (*Z*)-3-iodo-2-propenoic acid **304**,[199] subsequent DCC-DMAP mediated coupling with 3-(hydoxymethyl)-3-methyloxetane **303** gave **302** in good yields after distillation.

Attempts to trigger the rearrangement of **302** were unsuccessful however. A range of Lewis acids were tried (BF_3-Et_2O, nitrophenylboronic acid, $Cu(OTf)_2$, $Sn(OTf)_2$, $Ti(iOPr)_4$), but none gave satisfactory results and led to decomposition and multiple products on TLC; it is likely that the Lewis acids needed to trigger the rearrangment are incompatible with the iodide function of **302**.

Because this route directed towards the use of OBO-esters seemed problematic, the focus was switched to obtaining the corresponding ABO-esters, as a literature survey and information divulged had suggested that these may be more suitable, being generally more robust (ABO-esters are tolerant to acidic conditions whereas OBO-esters are rather acid sensitive, with the carboxylic acid function being returned under even mildly acidic conditions), and it is also known that the rearrangement of their

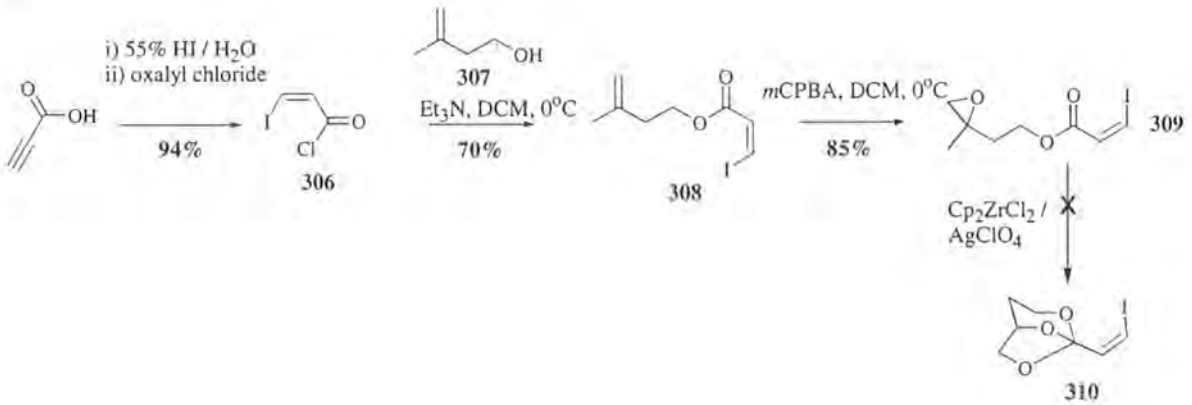
epoxyester precursors (which occurs with mild Lewis acids such as zirconocenes) is tolerant of halides.[200]

Figure 26. Crystal structure of OBO-ester **301**.



This intimated that the ABO-esters might be a superior alternative anyway, and synthetic efforts were directed towards **310**, the ABO-protected analogue of **214**, as indicated in scheme 62.

Scheme 62



Accordingly, hydroiodination of propiolic acid and treatment of the (*Z*)-iodoacid with oxalyl chloride gave **306** in excellent yield. This was then coupled with alcohol **307** to provide the ester **308**, which was itself converted into epoxy-ester **309** by standard methodology. Sadly, again the rearrangment to give the orthoester could not

be realised; use of the advocated Lewis acid $Cp_2(Cl)Zr^+$ (generated *in situ* upon mixing $Cp_2(Cl_2)Zr$ with the sequestrate $AgClO_4$) failed to induce the rearrangement, and a similar selection of Lewis acids as used before to attempt the rearrangement of **302** to **301** gave poor results, mostly giving complex mixtures of products, or returning starting material. Having arrived at what seemed like a synthetic impasse, little choice was left but to return to the original strategy, and attempt to perform the Heck reaction between **214** and **122** using bases that would not undergo the Michael addition-elimination sequence.

2.4.2.3 Further palladium reaction screens.

A Heck reaction involves a greater number of variables compared to many synthetic processes; even when coupling partners are kept constant, varying the base, palladium source, ligand, catalyst loading, solvent, additives (*i.e.* halide scavengers or phase-transfer catalysts) and reaction temperature and pressure will generate a vast number of conditions for screening. Nevertheless, it was realised that because of the limited freedom with regards choice of base imposed by the side-reaction described above, it would be necessary to perform as comprehensive a screen as possible, and investigate many of the conditions implemented in the chase for the highest activity, such as use of bidentate ligands, direct sources of palladium(0), and perhaps even phosphine-free systems.

From the previous study, it had been discovered that *N,N*-diethylaniline **289j** was reluctant to undergo this addition-elimination reaction, no doubt due to its steric bulk.

This base, together with a number of others, was incorporated into a comprehensive screen in which all manner of ligands, solvents and palladium sources were employed. The conditions that were varied in the 150 or so screens performed in attempting to obtain conditions that would give a successful Heck reaction between **214** and **122** are listed in table 14, but only as a matter of reference, because disappointingly, and perhaps surprisingly, not a single combination of variables gave rise to a successful Heck product.

The palladium sources tested varied from the standard palladium acetate to the more complex palladacycle Hermann's catalyst,[201] derived from tris(*o*-tolyl) phosphine and palladium acetate; similarly, ligands employed ranged from the standard

monodentate phosphines such as triphenyl- and tris-(furyl) phosphine, to ligands such as tri-*t*-butyl phosphine and a selection of bidentate phosphines of varying bite angle.[202] Additionally, more esoteric catalytic species such as [bis(diphenylphosphino)ferrocene] dichloropalladium(II) and tris(dibenzylideneacetone) dipalladium(0)-chloroform[203] adduct were used. Neither the latter, nor tetrakis(triphenylphosphine) palladium(0), both sources of nucleophilic palladium(0) and therefore often found to offer higher reactivity, proved to have any bearing on the reaction.

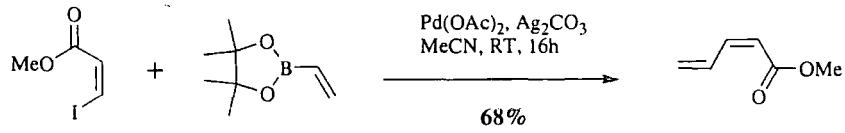
Table 14: conditions tried in the Heck coupling between 214 and 122

Palladium sources (at loadings from 2.5-10 mol %)	$PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3.CHCl_3$, $Pd(dppf)_2Cl_2$, $Pd(MeCN)_2Cl_2$, $Pd(Bn)(PPh3)_2Cl$, Hermanns catalyst
Ligands	PPh_3, P(*o*-Tol)$_3$, P(*t*Bu)$_3$, P(*n*Bu)$_3$, P(Cy)$_3$, dppb, dppp, dppe
Additives	Ag_2CO_3, TlOAc.
Bases	Ag_2CO_3, K_2CO_3, benzylidene benzylamine, tetramethylurea, DBU, *N,N*-diethylaniline. NaOAc.
Solvents	THF, MeCN, PhMe, DMF
Temperatures	ambient to sealed tube conditions.

It was observed that when particularly forcing conditions were used (sealed tube conditions at >110°C for up to 4 days), the iodoacrylate underwent de-hydroiodination, presumably through the action of the base. It was abundantly clear when this happened; TLC was used as the principal means of assessing the progress / success of these screens, specifically, disappearance of **214** was used to identify a potential succesful reaction. Frequently in such cases it transpired that upon work-up, the crude ^{1}H NMR spectrum would show no alkene resonances. It was also observed that even *N,N*-diethylaniline would start to undergo Michael addition under such harsh conditions.

The only time coupled products were obtained was under phosphine-free conditions, and only then when the base silver carbonate was used. In this instance, the Suzuki product **311** was obtained as the exclusive product as represented in equation **18**.

Equation 18



214 **122** **311**

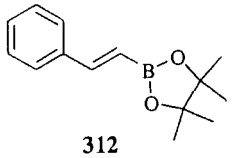
This result is not particularly surprising; the only examples of couplings of haloacrylates with organoboron partners in the literature show conversion to Suzuki

products in every instance and under similar conditions to those employed in this example.[204]

Indeed, it is known that halide scavengers can accelerate Suzuki reactions by facilitating the exchange of halide for base at palladium in the species obtained from oxidative addition leading to intermediates with enhanced reactivity, and conventional wisdom also upholds that inorganic bases such as carbonates will nearly always favour a Suzuki pathway by activation of the organoboron reactant towards transmetalation.

To check whether **214** was indeed capable of undergoing Heck coupling with *any* alkene, a separate series of experiments was carried out with hex-1-ene and the archetypal Heck alkene, styrene. These experiments were all done under conditions that most commonly give rise to Heck products ($Pd(OAc)_2$, DBU or *N,N*-diethylaniline, toluene reflux), yet no evidence of coupling was seen in any of these reactions.
A further observation is that when forcing conditions were employed in these reactions in conjunction with triphenylphosphine, oftentimes styrylboronate **312**[98] was produced (figure 27)

Figure 27



312

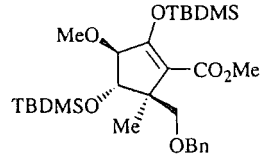
In light of the reagents used, only one possible explanation exists for the production of this compound, and it does not bode well for the utility of **214** as a Heck iodide. Such compounds as **312** are the result of oxidative insertion by Pd(0) into the C-P bonds of the ligand, and thus are usually taken as a sign of poor substrate reactivity;[187a] exactly as was found to be the case here, where the only coupling evident was one where the conditions both cultivated a highly reactive catalytic engine and favoured the following of a thermodynamic pathway towards **311**.

2.4.3 Routes towards the core cyclopentenol 211.

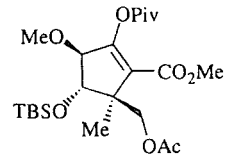
2.1.1.1 Existing syntheses in the literature.

It should first be acknowledged that viridenomycin's core cyclopentenol has been the subject of recent attention, with two reported syntheses in the last three years. The first, reported by Meyers and co-workers,[205] details the construction of **313** and involves at least eighteen stages giving an overall yield of 40%, with the key step exploiting the templating ability of a chiral bicyclic lactam to install the quaternary stereocenter at C_{10}.

Figure 28



313



314

The second reported synthesis[206] uses a markedly different strategy involving a highly functionalised tetrahydrofuran derived from D-glucose. Using this strategy, the authors accessed compound **314** in twenty three individual operations (yield was not reported), which they then converted to Meyers' product **313** for comparison.

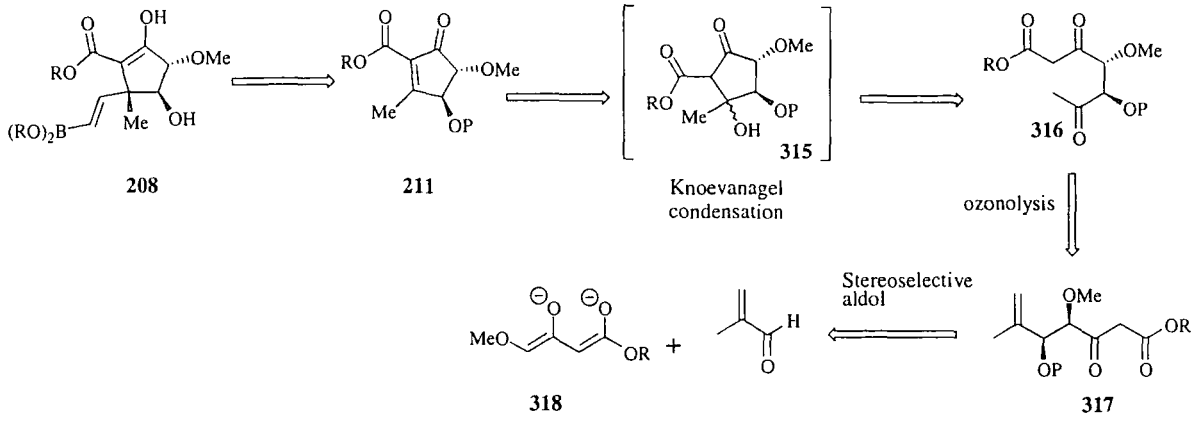
Although there are consequently two successful syntheses of the core already in the literature, it was felt that both strategies are rather long and unnecessarily elaborate, and it would be more satisfying to devise a new route utilizing different chemistry.

2.1.1.2 Our approach based on the enantioselective Mukaiyama aldol reaction.

The route that was developed, which hinged upon a stereoselective aldol reaction to install the crucial stereochemistry of **211**, is outlined by way of the retrosynthetic scheme shown in figure **29**. In this approach, a stereoselective aldol addition of a dienolate equivalent **318** to methacrolein would provide aldol **317**; ensuant oxidative cleavage of the double bond of **317** would yield ketone **316**. It was imagined

this ketone would be ideally poised to cyclize to give the desired enone **211** in a Knoevanagel condensation, *via* spontaneous dehydration of **315**.

Figure 29



As eluded to above, the pivotal reaction in this sequence in terms of securing the correct diastereomer of **211** was to be the stereoselective aldol, and choice of reaction type here was not difficult to make in light of literature precedent.

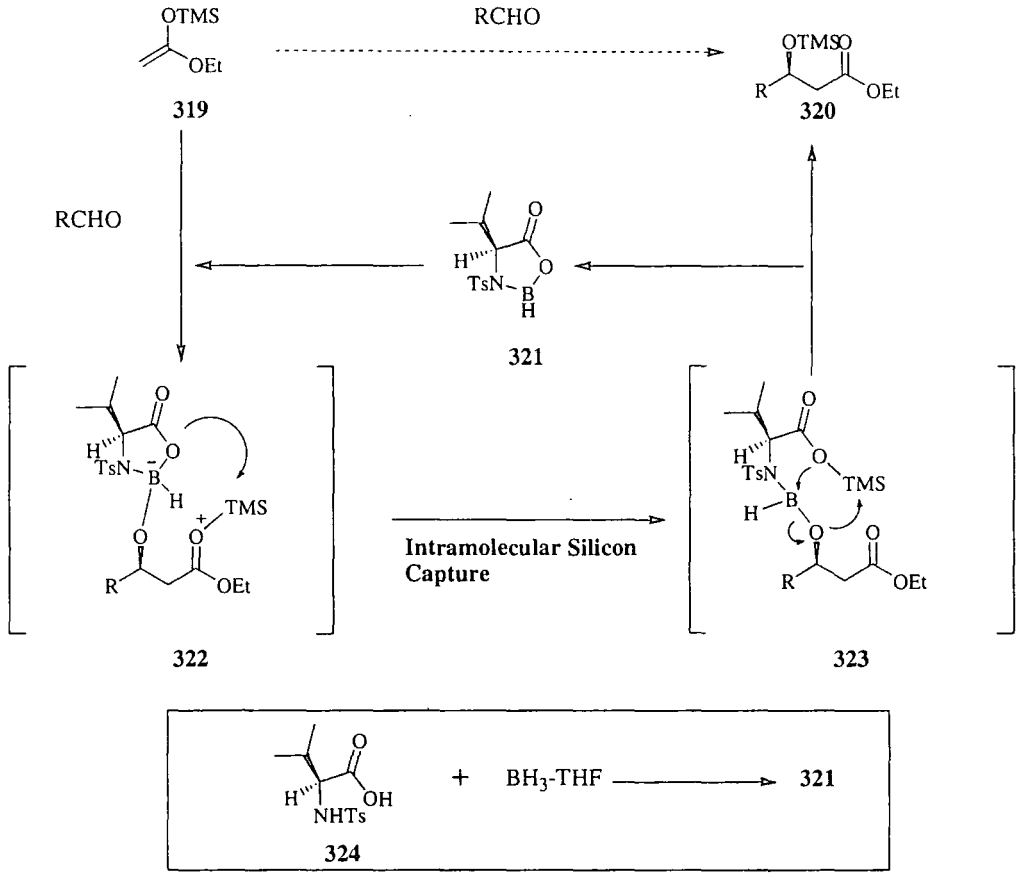
The Mukaiyama aldol reaction,[207] the preeminent example of a C-C bond forming process between a latent enolate equivalent and an activated acceptor, is a much-used and well-studied reaction.[208] It is attractive since its procedural requirements entail the separation of the enolization process from the actual C-C bond addition reaction. Moreover, use of silyloxyalkenes (silyl enol ethers) in the reaction requires the intervention of a suitable Lewis acid catalyst to coordinate to and activate the acceptor towards nucleophilic attack, and this catalyst can also serve as a vehicle by which to achieve stereoselection.

Having chosen the type of aldol reaction, it was necessary to select which of the many catalytic variants of it to employ, and the degree of freedom in making this choice was slightly limited by the nature of the electrophile. Use of copper complexes as chiral catalysts (for instance, the well-studied Cu-BOX and Cu-PyBOX systems) was precluded since it is known that an α-substituent capable of chelating copper is required on the acceptor. Of the other commonly employed systems, the chiral oxazaborolidinones derived from *N*-sulfonlyamino acids and borane seemed attractive due to the relative simplicity of their preparation and stability compared to other more elaborate systems based on titanium(IV), tin(II), gold(I) or silver(I); in addition, there was a wealth of literature detailing the successful deployment of the oxazolidinone-

mediated Mukaiyama aldol reaction, sometimes giving aldol products with near-perfect enantioselection.[209]

The operation of the Mukaiyama reaction, exemplified by a typical case shown in scheme 63, revolves around the five-membered boron heterocycle **321** generated by the combination of 1 equivalent of N-Ts-D-valine **324** and borane.

Scheme 63

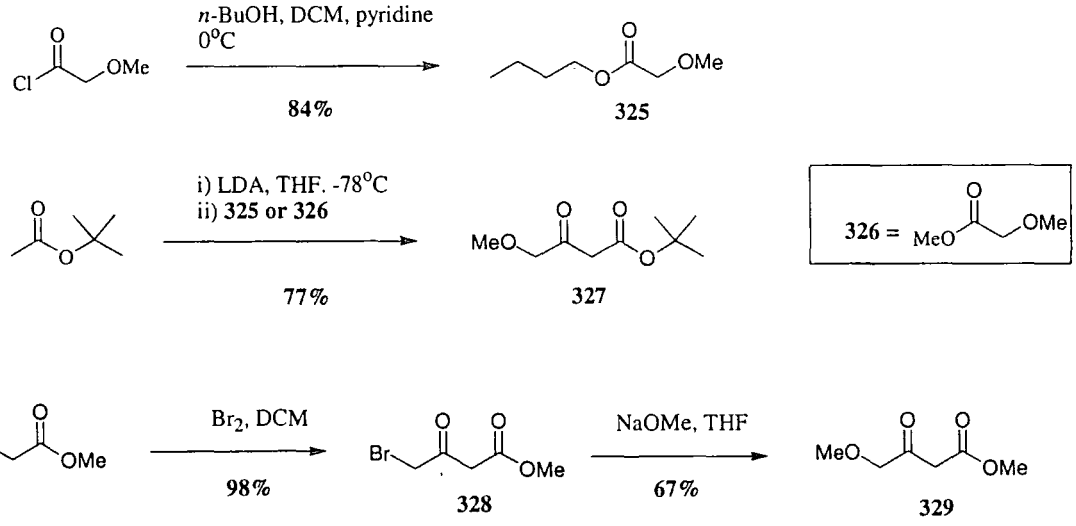


Unlike certain other metal catalyzed aldol reactions, the use of an oxazaborolidinone complex is purported to effect operation of an active mechanism to ensure efficient scavenging of electrophilic silicon species generated from the catalytic cycle. Such intramolecular silicon transfer is known to be crucial in order to achieve efficient transfer of chirality and catalyst regeneration, and proceeds in the following manner: the silyl oxocarbenium ion **322** produced *via* the nucleophilic addition of **319** to RCHO places the boron carboxylate in a position to effect intramolecular silicon transfer, generating boron aldolate **323**. Rearrangement of this aldolate, with concomitant regeneration of the five-membered catalytic boron heterocycle **321** and

silicon transfer to generate silyl aldol adduct **320**, effectively precludes the incidence of enantioselectivity-reducing achiral silicon catalysis.[210]

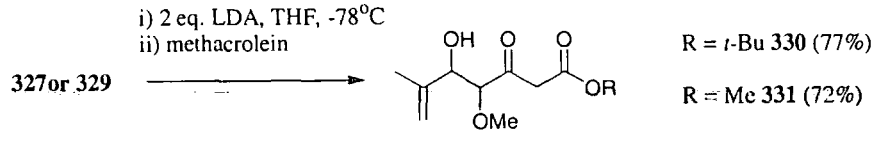
Having opted to use a Mukaiyama aldol to install the requisite stereochemistry of the core **208**, it was necessary to prepare a suitable enolate equivalent **318**, but first, a prescient achiral pathway was explored, both to generally test the methodology and stability of the aldol **317**, and also to test the stability of **317** towards ozonolysis. This required the synthesis of β-keto esters **327** and **329** from which to generate the requisite dienolates **318**, since despite their utility, there were relatively few β-ketoesters commercially available (scheme 64). For simplicity and ease of preparation, the *t*-Bu β-ketoester was generally preferred throughout the studies towards the core cyclopentenol **211**; additionally, using a *t*-Bu ester seemed sensible given that the core was to be tethered to the southern hemisphere tetraene by a macrolactonization, requiring removal of this ester.

Scheme 64



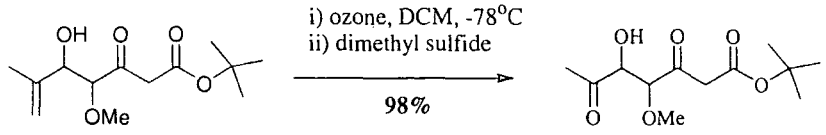
Having obtained **327** and **329** using rather straightforward chemistry, aldol reactions were carried out by generation of the lithium dienolates of both β-ketoesters, and the subsequent reaction of these with the chosen electrophile methacrolein (equation 19).

Equation 19



Happily, both aldol adducts **330** and **331** appeared stable, and an ozonolysis was then attempted on the favoured *t*-Bu adduct **330** (equation 20).

Equation 20

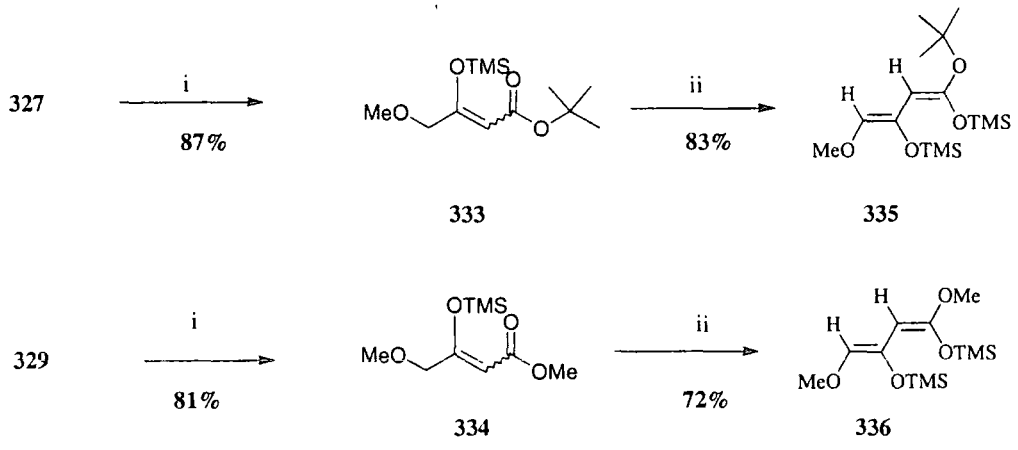


330 **332**

Gratifyingly, the ozonolysis produced dione **332** virtually quantitatively after reductive work-up with DMS, and encouraged by these results, it was elected to attempt the preparation of suitable latent enolates equivalents of **327** and **329**, which called for the synthesis of 1,4-dimethoxymethoxy-bis(TMS)-1,3-butadienes **335** and **336** according to a procedure described by Brassard *et al.*, who had made and prepared **336** for use as a reactive diene in cycloaddition reactions aimed at purpurin synthesis (scheme 65).[211]

In this method, the β-ketoester is activated with a Lewis acid and then treated with base and TMS-Cl under thermodynamic conditions, producing the intermediate silyl enol ethers **333** and **334** as a 50:50 mixture of geometric isomers. These are then isolated and treated with LDA and TMS-Cl under kinetic conditions, affording the 1,4-dimethoxy-bis(TMS)-1,3-butadienes **335** and **336** in good yields following direct distillation from the reaction, after first filtering to remove the amine hydrochloride salt.

Scheme 65



i) $ZnCl_2$, Et_3N,TMS-Cl, PhMe, 45°C
ii) LDA, -78°C, THF, then TMS-Cl

The utility of these novel dienes in the Mukaiyama aldol reaction was confirmed by their successful reaction with methacrolein, mediated by oxazaborolidinone **321**, generated *in situ* from borane-THF and N-Ts-D-valine.

However, it was noted that after aqueous work-up, silylated products were being obtained, and as stirring with $NaHCO_3$[212] failed to effect efficient desilylation, the Carreira procedure,[213] which entails treating the crude silylated aldols with TFA-water at -78 °C, proved to be effective and provided **330** and **331** in good yields (76 % and 66 % respectively).

This desilylation procedure proved to be troublesome if it was not performed at low temperature; treatment at just 0 °C gave rise to retro-aldol products, thus β-ketoester **327** would be produced from the reaction between **335** and methacrolein, presumably as a result of retro-aldol from the *O*-silylated aldolates.

Having obtained good results with the reaction of methacrolein and **335**, a range of electrophiles were examined to determine the scope and utility of this transformation, since aldol reactions of 1,4-dimethoxy-bis(TMS)-1,3-butadienes are unreported.

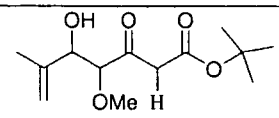
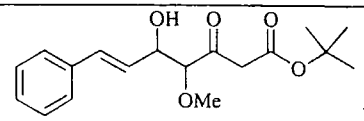
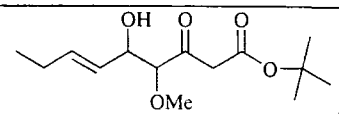
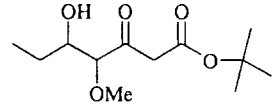
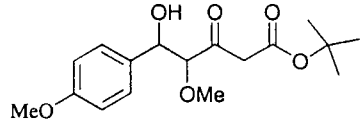
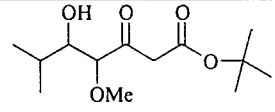
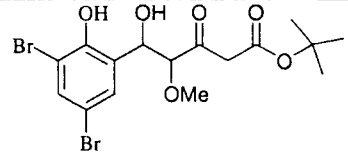
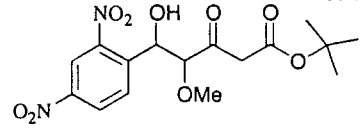
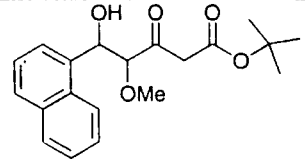
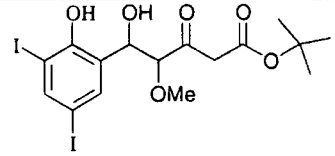
Table 15 presents the results of this study, and the data suggests that these dienes are powerful nucleophiles in the Mukaiyama aldol reaction, affording good results with both sterically hindered aldehydes, and also those having electron-donating R groups.

Obviously it was necessary to now probe the selectivity of these reactions, given that the requirement for the synthesis of the core was a *syn* selective aldol. However, and most disappointingly, discerning the ratio of diastereomers proved an impossible task, although not for want of trying!

The first thing to note is that the ^{1}H and ^{13}C NMR data suggests a single major diastereomer. However, it was noted that all of the carbon environments on the ^{13}C NMR spectrum exhibited 4 resonances clustered around a particular value of δ, each of varying intensity, although there was in each case 1 dominant signal more intense than the others. Additionally, there appeared to be unclassifiable extra resonances not ascribable to the aldol adducts, that were still visible even after careful purification.

Given the nature of the catalytic system employed in this reaction, 4 resonances close together for each carbon environment (implying 4 unique stereoisomers) seems an unusual observation. Unlike many other catalytic systems where the Lewis acidic metal gives rise to a tight 6-membered closed transition state, it is known that the Mukaiyama aldol reaction proceeds *via* an open anti-periplanar transition state.[214]

Table 15: aldol reactions between diene 335 and a range of electrophiles.

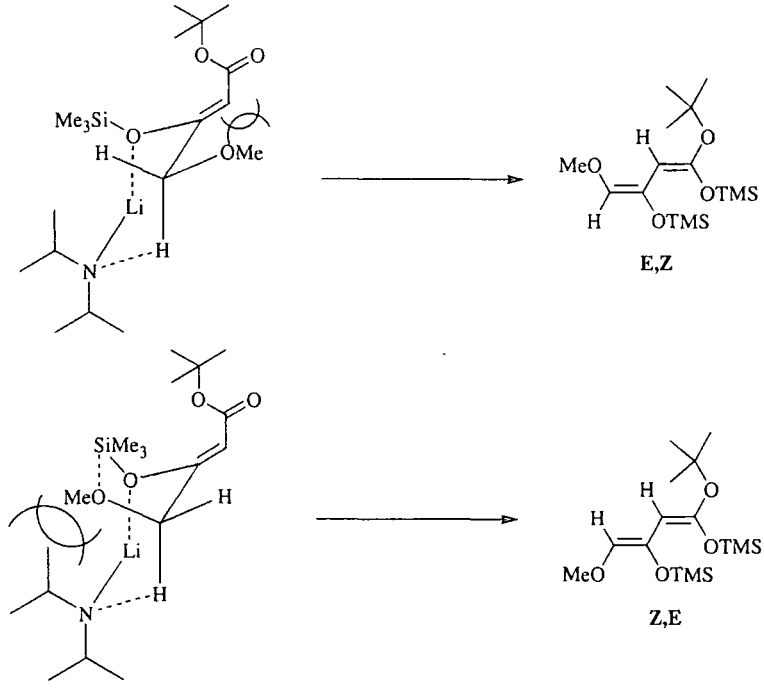
Electrophile	Aldol adduct	Isolated yield
methacrolein	 **330**	76 %
trans-cinnamaldehyde	 **337**	90 %
trans-2-pentenal	 **338**	77 %
propionaldehyde	 **339**	72 %
para-anisaldehyde	 **340**	78 %
isobutyraldehyde	 **341**	67 %
3,5-dibromosalicylaldehyde	 **342**	80 %
2,4-dinitrobenzaldehyde	 **343**	88 %
1-naphthaldehyde	 **344**	72 %
3,5-diiodosalicylaldehyde	 **345**	83 %

Conditions: 1 mole electrophile per mole of diene, 25 mol % **321**, DCM, -78 °C, 2-6h. Desilylation achieved with 10% TFA-water at -78 °C.

Due to the nature of this transition state, in which it is imagined that the nucleophile and electrophile approach in such as way as to minimize torsional

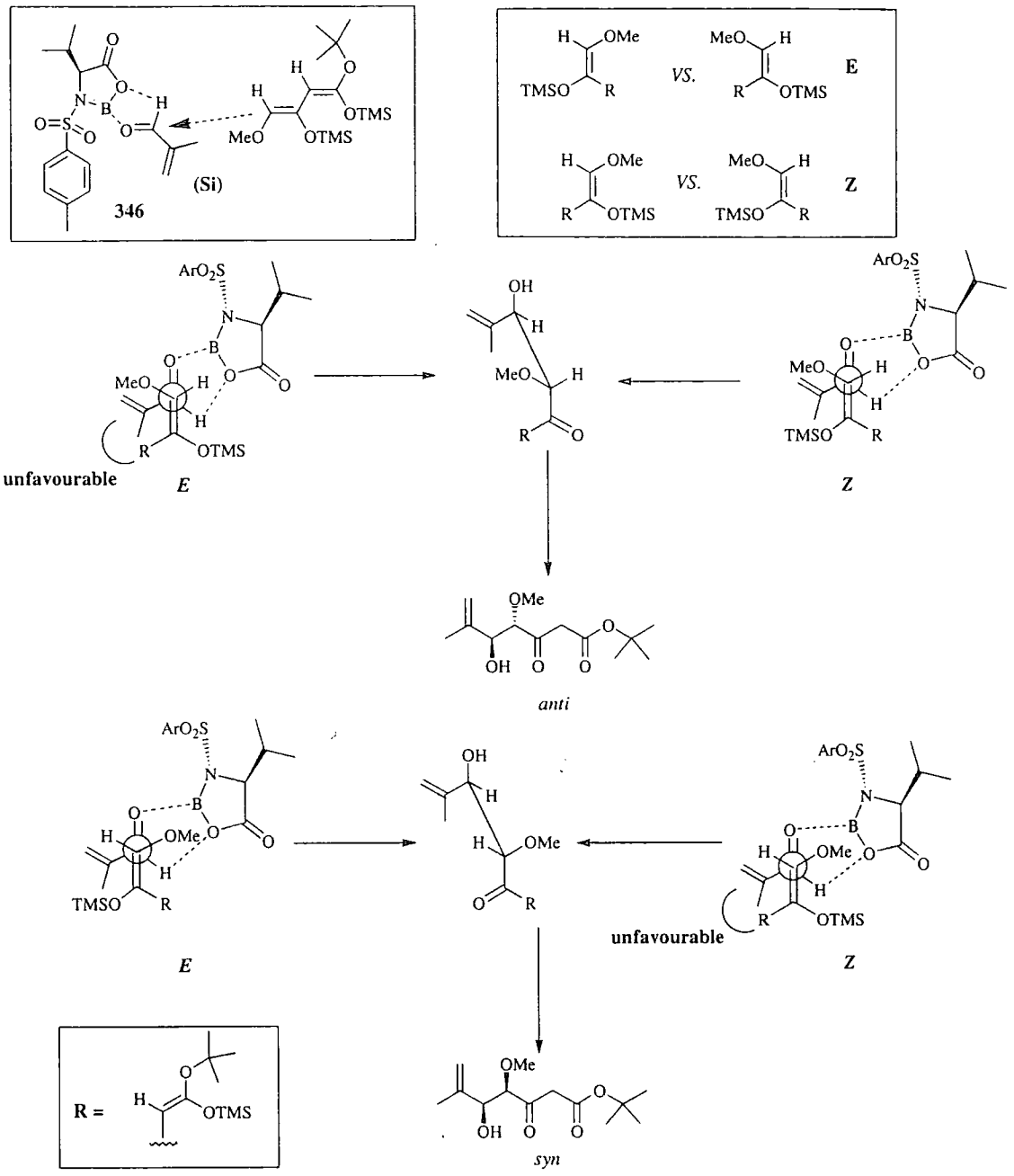
interactions, the geometry of the silyl enol ether is not nearly so influential as it is in, for example, a Sn(II) mediated process; instead, the *syn* : *anti* ratio is heavily influenced by nucleophile structure. Thus, it is eminently possible to get a *syn* aldol adduct from both (*E*) and (*Z*) silyl enol ethers. In any case, it is difficult to predict which double bond geometry of **335** was installed during the enolization procedure under kinetic conditions (scheme 65); even if the application of the Ireland-Claisen model[215] to this particular case was appropriate, scheme 66 reveals that there is not a great bias towards either enol geometry, and LDA is known to have intermediate influence in determining enol geometry anyway.

Scheme 66



The rationalization of the stereochemical outcome in the reaction of either (*E*,*Z*)-**335** or (*Z*,*E*)-**335** is shown in scheme 67, where, considering only the reactive double bond, it can be seen that only two aldol products are possible, since the catalytic species **321** binds the aldehyde in such a way as to permit the nucleophile to approach via the *Si* face only. It then becomes a question of examining the 4 possible transition states that arise from the reaction of each face of either the (*E*) or (*Z*) silyl enol ethers, and since the configuration at one of the new stereocentres is completely controlled by steric effects due to the catalyst-electrophile complex **346**, only two outcomes are possible: *syn* and *anti* diastereomers (it should be noted that the transition state models in scheme 67 do not consider the possible influence of any chelation effects.)

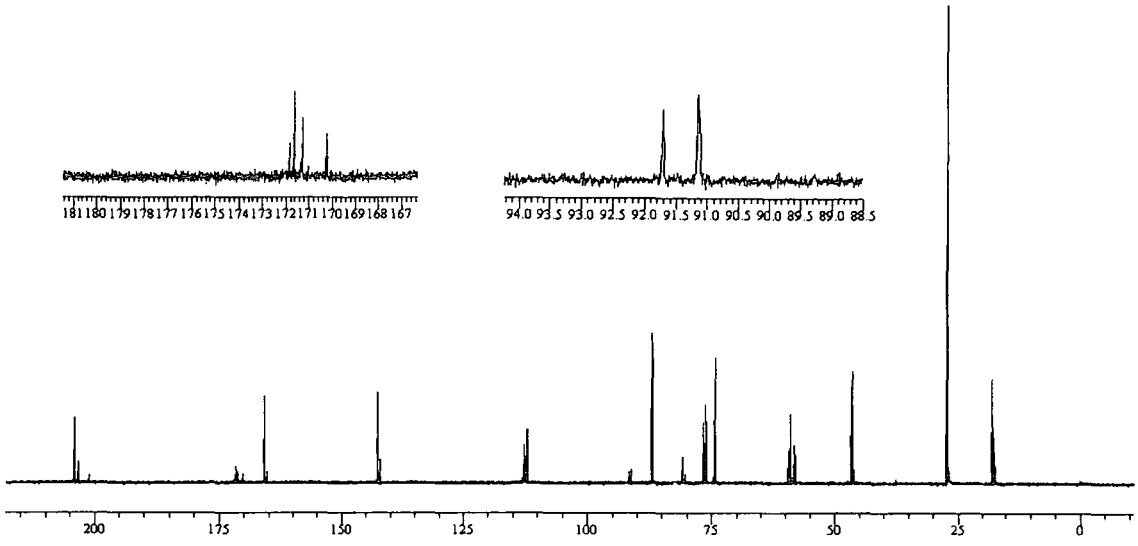
Scheme 67



This makes the observation of 4 unique NMR environments for each carbon atom seem puzzling, however, a possible explanation for this can be found by examining the ^{13}C shifts carefully.

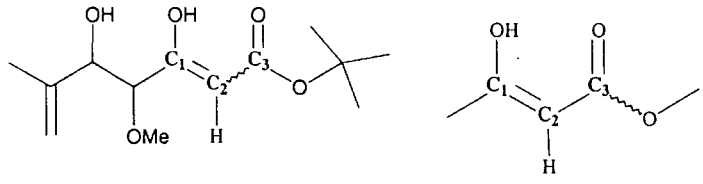
The ^{13}C NMR spectra of adduct **330** is shown in figure 30, together with the expansions of the region around δ 170-175 and δ 88-92. Both regions shows resonances not readily attributable to compound **330**, but instead, strongly suggest enol tautomerization of this aldol product.

Figure 30 ^{13}C NMR spectrum of **330**



DEPT analysis assisted the assignment of these extraneous resonances as illustrated in table 16, and the assumption of (*E*) / (*Z*) enol tautomers is validated by comparison alongside literature values for a typical enol tautomer of a β-keto ester **347** (figure 31).[216]

Figure 31



330 **347**

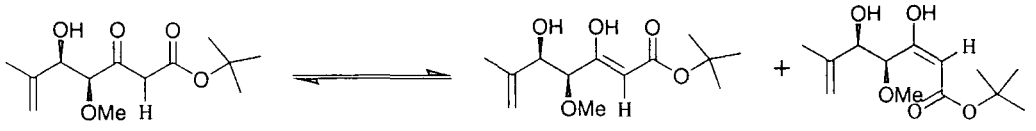
Table 16: comparision between certain ^{13}C NMR shifts for 330 and that of a standard enol tautomer

Carbon number	DEPT analysis	δ / ppm in **330**	δ / ppm in **347**
1	quaternary	171.80; 171.60	177.5
2	methine	91.14; 91.69	90.5
3	quaternary	170.19; 171.24	174.7

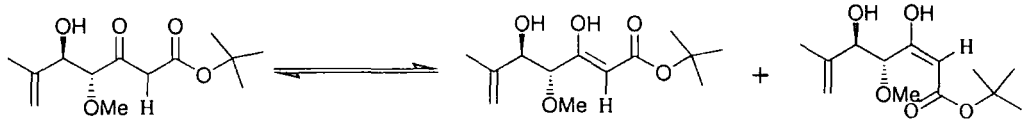
The explanation for the 4 resonances becomes apparent in light of this supporting information; the aldol adducts are produced as a mixture of *syn* and *anti* diastereomers, with a low equilibrium concentration of enol tautomer also being observed for both these diastereomers, giving rise to what at first glance look like minor

impurities in the spectrum (scheme 68). The groups of 4 resonances clustered together are due to conformational differences in the species present, which give rise to minor changes in the carbon environments, whilst those at δ ~90 and δ ~170 are clearly in different environments, as would be expected since the carbon atoms responsible for these signals have undergone configurational changes upon tautomerization.

Scheme 68



syn-330



anti-330

It is the problem of enol tautomerization that made it very difficult to measure the *de* for the aldol reaction. The first line of approach was to use chiral HPLC to determine the ratio of diastereomers, and separation conditions were employed based on functional group correlation between the aldol products and known compounds whose separation methods had been reported in the literature.[217]

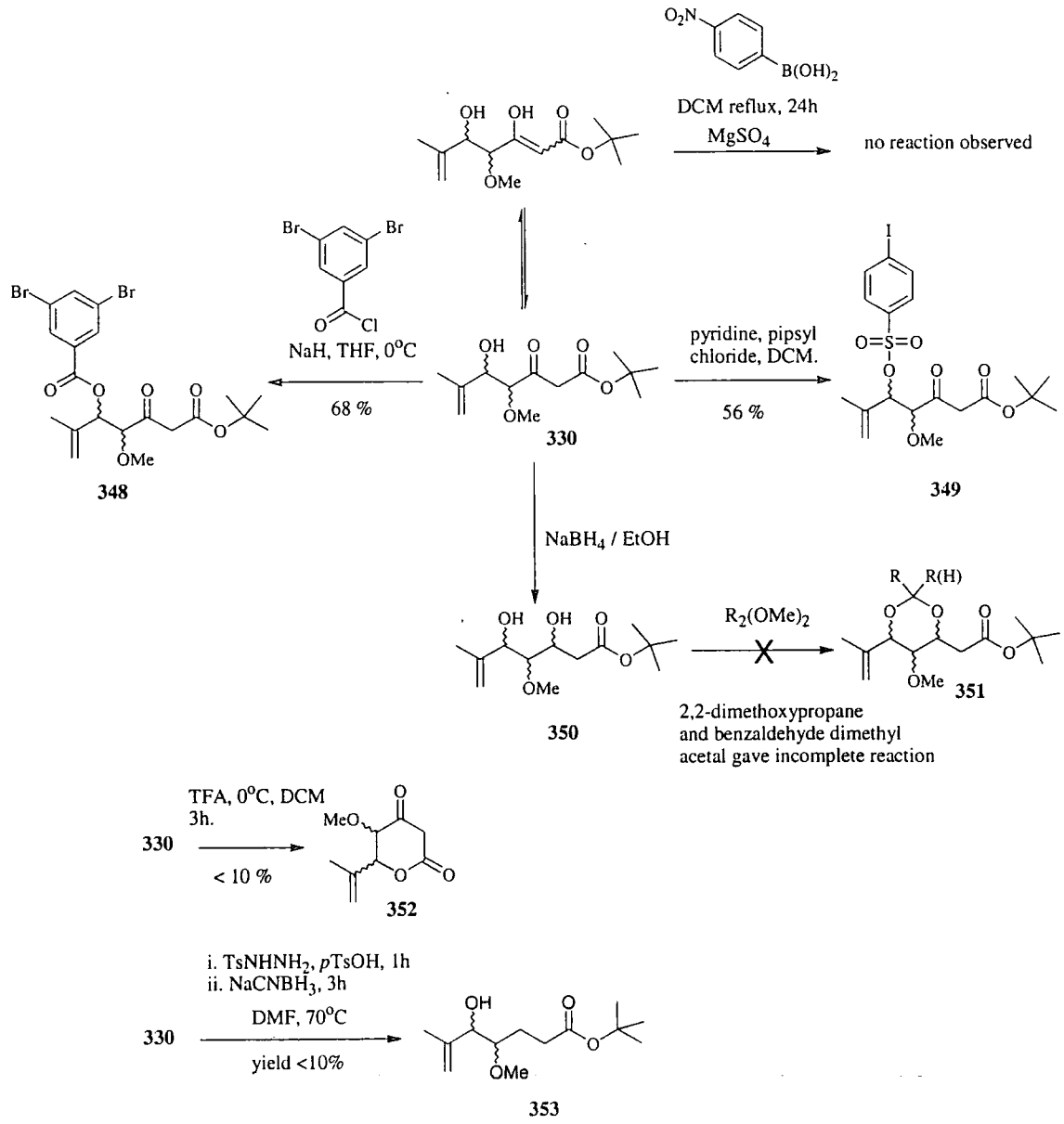
Chiral HPLC proved unsuccessful; pure samples of **330** gave rise to peaks that were either too broad, that overlapped completely, or with some solvent systems, gave rise to numerous poorly defined peaks (conditions are shown in table 17).

A number of other strategies were tried in order to determine the diastereomeric ratio, as summarized in figure 32. In first approach, it was attempted to try to prepare a "heavy" derivative of **330** that would hopefully be crystalline, hence enabling the configuration of the major diastereomer to be identified by XRD. To this effect, the bromobenzoate ester **348** and pipsylate **349** were prepared by functionalization of the aldol hydroxyl group with 3,5-dibromobenzoyl chloride and 4-iodobenzenesulfonyl chloride respectively. It was noted that using amine bases (*e.g.*, pyridine or TEA) in attempting to form **348** led to formation of the acid anhydride rather than esterification. Unfortunately neither of these compounds were crystalline, instead being isolated as viscous oils.

Table 17: HPLC conditions tried in order to determine the stereoselectivity of the aldol reactions

Solvent system	Flow rate / ml min^{-1}	Column
95:5 hexane / EtOH + 0.01% TFA	1.0	Chiralpak AD
95:5 hexane / EtOH + 0.01% TFA	0.5	Chiralpak AD
95:5 hexane / EtOH + 0.01% TFA	0.25	Chiralpak AD
1, 3,5 and 10% IPA / Hexane	1.0	Chiralpak AD
1, 3,5 and 10% IPA / Hexane	0.5	Chiralpak AD
1, 3,5 and 10% IPA / Hexane	0.25	Chiralpak AD
1, 3,5 and 10% IPA / Hexane	1.0	Chiralpak OD
1, 3,5 and 10% IPA / Hexane	0.5	Chiralpak OD
1, 3,5 and 10% IPA / Hexane	0.25	Chiralpak OD

Figure 32



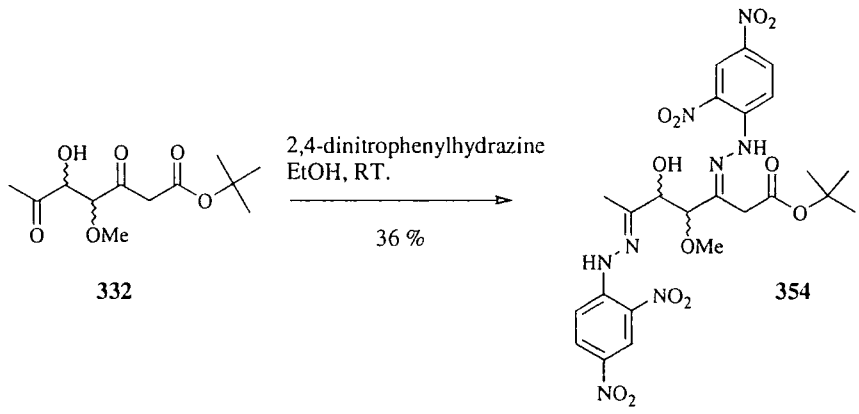
Attempts were also made to 'lock' the conformation of the aldol adducts by preparing a 6-membered boronate ester derivative through reaction of **330** with 4-nitrophenylboronic acid, hoping that the thermodynamic stability of such a boronate ester would ensure complete reaction and that it would be possible to determine the configuration at the new stereocentres by either measuring the ^3J coupling constants for the ring protons, or performing NOE studies. However, no reaction was observed even after forcing conditions were employed, *i.e.* prolonged reflux.

Continuing the theme of preparing a cyclic derivative of **330**, it was reported that treatment of similar adducts with TFA effects de-*t*-butylation and triggers their subsequent lactonization, and this procedure was carried out as described.[218] Although this furnished lactone **352**, the reaction was incomplete and led to a mixture of products and gave **352** in miniscule yield. Similarly, reduction of **330** with $NaBH_4$ / EtOH gave the diol **350** that could be converted into the acetals **351**, but again, the reactions never went to completion. It was observed that the intermediate diol **350** proved to be rather unstable, decomposing rapidly at room temperature and on silica, so for this reason the transformation **330**→**351** was attempted in a one-pot process.

It was suspected that these difficulties were due to the fact that what was ostensibly a pure compound by TLC was actually a mixture of several isomers, and since this problem arose because of enol tautomerization, it was elected to try to remove the ketone by a modified Wolf-Kischner procedure, using *p*-tosylhydrazide to give the intermediate hydrazone followed by *in situ* reduction with sodium cyanoborohydride.[219] Unfortunately, this also gave very poor yields of **353** and the crude ^1H NMR spectrum showed mixtures of products, including the intermediate hydrazone and even starting material **330**.

Attempts were also made to functionalize the ketone by converting it to a hydrazone that would hopefully be crystalline, and in order to add molecular weight, the aldol **330** was converted to the dione **332** with a view to obtaining the dihydrazone. It was found that simply stirring **332** with a solution of 2,4-dinitrophenylhydrazine in ethanol at ambient temperature gave the dihydrazone **354**, albeit as a minor fraction, but regrettably (and rather astonishingly!) even this high molecular mass compound was isolated as a bright yellow oil that defied attempts to recrystallize it. Despite removing the ketone and hence the capacity for enol tautomerization, the ^1H NMR spectra of **354** was still overly complicated and it was impossible to determine any information concerning the configurations at the chiral centres since the resonances were rather broad.

Equation 21

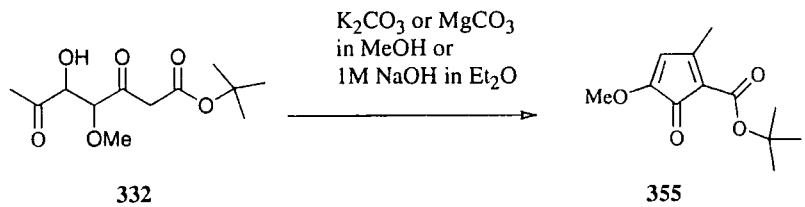


332 **354**

Having encountered considerable difficulties in trying to determine the diastereomeric ratio for the aldol reaction by derivatising the aldol adduct, it was decided to attempt the cyclization to the core **211**, and hence determine the *de* from this, either through functionalization or by comparison to the reported data for **314**.

There were no exact pertinent procedures in the literature to assist in selecting conditions for the Knoevanagel condensation of **332**, so instead a host of generic processes were tested. It was discovered that acid-base catalysts such as pyridinium acetate and triethylamine hydrochloride were ineffective; on the other hand, treatment with bases such as pyridine or piperidine, even in catalytic amounts and at lower temperatures, led to rapid decomposition of **332**, evident on TLC by the appearance of numerous components. The only reactions that appeared clean were those using inorganic bases, such as K_2CO_3 or $MgCO_3$ in MeOH (essentially a source of MeO^-), or dilute sodium hydroxide in diethyl ether. However, upon working these reactions up and isolating the major component, it became apparent that **332** was over-eliminating, since the NMR, IR and MS evidence strongly pointed towards cyclopentadienone **355** as being the major product (equation 22).

Equation 22



332 **355**

It was unfortunate that this difficulty could not be overcome during the time of this study, since it means that what appeared to be a reliable and expedient method for preparing the core of viridenomycin fails at the final hurdle.

2.5 Concluding remarks

As anticipated, viridenomycin **11** proved to be a formidable synthetic challenge and there is much work still to be done in order to complete the total synthesis. Despite the fact that viridenomycin was chosen as a candidate with which to further test the palladium coupling methodology developed in these laboratories, it actually transpired that very little palladium coupling chemistry was performed, such were the problems encountered both in attempting to acquire the requisite halide coupling partners in the case of the southern tetraene **210**, and with one of the partners itself in the case of the northern triene **209**. This highlights the need to perhaps adopt an alternative strategy with respect to the latter fragment.

Nevertheless, considerable in-roads were made towards achieving the synthesis of **11** and these studies called for the development of new chemistry, and the need to improve on existing chemistry. Most notable was the development of new aldol chemistry used in the approach to the core cyclopentenone **211**, and the greatly improved procedures developed *en route* to the southern hemisphere **210** which were based around phenylglycine, but which should be readily applicable to any amino acid.

2.6 Further work

As alluded to above, the preparation of the northern triene **209** may require a rethink; it might be necessary to reduce iodoacrylate **214** to the iodoalcohol, couple this alcohol with a vinylboronate and then perform the iodo-deboronation procedure. Carrying out a mild oxidation later on to return to the required acid oxidation level at this stage should allow this triene to be assembled free from the problems associated with using a Michael acceptor in the Heck reaction.

Two problems came to light in attempting to synthesize the core **211**. The first of these concerns the determination of the *de* from the Mukaiyama aldol reaction. The NMR evidence suggests tautomers of a major diastereomer, in which case it may be necessary to pursue the idea of removing the ketone function that gives rise to tautomerization. More attractive perhaps is employing one of the chiral silylation reagents recently reported by Meinwald and co-workers,[220] which should enable the de to be determined after the aldol reactions by functionalization of the aldol hydroxyl with a suitable chiral silyl derivative. Alternately, it may be possible to use MTPA ester methodology.[221]

Yet another approach may be to further investigate chiral HPLC as a means of determining this *de*; although a range of conditions was examined, this was by no means comprehensive and a recent paper has come to light which describes the preparation of similar aldol adducts from Chan's diene[222] that may offer a potential solution, and at least affirms the belief that it should be possible to separate aldol diastereomers such as **330** using HPLC.[223]

Concerning the southern tetraene **210** and the problems encountered with trying to progress beyond dienylboronate **268**, if indeed the problem was the labile nature of the Boc protecting group in the presence of ICl, a simple solution may be to try a more robust protecting group, or else use a milder source of I^+. Given the sensitivity and capricious nature of some of the amino acid functional group transformations that went into building **268**, the former suggestion may not be easy.

3.0 Experimental Section

3.1 General Experimental Details

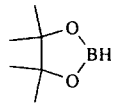
^{1}H NMR spectra were recorded on Bruker AC200, AC300 and AC400 instruments and on Varian 200, 300 and 500 model spectrometers at frequencies of 200-500MHz in d-chloroform unless otherwise stated. ^{13}C NMR spectra were recorded on the same instruments at 75.5, 100 or 125.5MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS. EI (70 eV) and CI mass spectra were performed on Kratos MS25, Micromass Autospec or Finnigan MAT XP 95 spectrometers. ES mass spectra were recorded on Finnigan MAT 900 XLT and Micromass Autospec spectrometers. FAB spectra were recorded on a Kratos MS50 using meta nitrobenzyl alcohol matrix; high resolution spectra were obtained from either Kratos Concept IS, Finnigan MAT 900 XLT or Micromass Autospec spectrometers. IR-spectra were recorded on a Perkin-Elmer 298 spectrometer. Melting points were determined using an Electrothermal melting point apparatus. Column chromatography was achieved under medium pressure using Acros silica gel, 60 mesh. TLC was carried out on Fluka Kieselgel $60F_{254}$ aluminium backed plates, visualization was achieved using either phosphomolybdic acid, ethanolic vanillin, or alkaline $KMnO_4$. $[\alpha]_D$ values are given in deg $cm^2 g^{-1}$ and were recorded at the D line of sodium (589 nm) in a 1 dm cell unless otherwise stated.

All glassware was dried in an oven and cooled under a stream of argon when an inert atmosphere was required. Exhaustive deoxygenation was achieved by the freeze-pump-thaw method (3 cycles); standard degassing was achieved by sparging with argon for 2 hours. Chemicals were obtained from commercial suppliers and were used without further purification unless otherwise stated. Carbonylchlorobis(triphenylphosphine) rhodium(I) and tri-*t*-butylphosphine were supplied by Alfa. Hermann's catalyst was supplied by Lancaster Synthesis. Polystyryl diphenylphosphine was obtained from Aldrich. Tetrakis(triphenylphosphine) palladium(0) was prepared according to a published procedure.[224] Benzaldehyde was pre-dried over anhydrous calcium chloride and distilled prior to use. *p*-toluenesulfonyl chloride was purified by dissolving in the minimum quanitity of diethyl ether, washing with 5% NaOH until the organic phase was colourless, drying the ether layer over $MgSO_4$ and finally recrystallizing at -78 °C. Methanesulfonyl chloride was distilled from P_2O_5 and stored under argon.

Diisopropylamine and triethylamine were distilled from CaH_2 onto KOH pellets. Dry solvents were obtained by distillation from CaH_2 (dichloromethane, hydrocarbons), magnesium and iodine (methanol and ethanol) and sodium/benzophenone (THF and Et_2O). Anhydrous DMSO and DMF were purchased from Aldrich. Pet. ether refers to the fraction boiling in the range 40-60 °C.

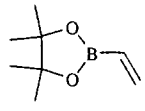
3.2 Specific Experimental Details

Preparation of pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane)[117]



To a solution of anhydrous pinacol (2.36 g, 20 mmol) in dry DCM (2 mL) stirred at 0°C under argon was added $BH_3.SMe_2$ (1.89 mL, 20 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 hour, and then stirred at room temperature until no further evolution of hydrogen was observed. Kugelrohr distillation (20 mmHg) gave pinacolborane as a colourless clear liquid; analytical data was consistent with that reported in the literature.

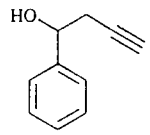
4,4,5,5-Tetramethyl-2-vinyl-1,3,2-dioxaborolane 122[see 185]



Vinylmagnesium bromide (100 mL of a 1.0M solution in THF, 100.0 mmol) was added dropwise to a stirred solution of anhydrous trimethylborate (10.2 mL, 90 mmol) in dry THF (170 mL) at -78 °C under argon. The solution was stirred for a further hour, then allowed to warm to room temperature. 20 % HCl (44 mL) was added, and the mixture was stirred for 10 minutes. A solution of pinacol (10.6 g, 90 mmol) in diethyl ether was added, and the reaction was stirred for a further hour. The aqueous layer was extracted with diethyl ether (100 mL) and the organic layers washed with saturated Na_2CO_3 (2x100 mL) and water. Double distillation of the organic layer gave pure **122** (8.22 g, 53%) as a clear colourless liquid; b.p.115-120°C (760 mmHg); ν_{max} (neat)/cm^{-1} 3100 (medium, olefinic C-H str.), 3000 (strong, aliphatic C-H str.), 1625 (strong, C=C str.), 1450 (strong, aliphatic C-H def.), 1380 (strong, doublet, $-C(CH_3)_2$), 1330 (very strong, B-O str.), 1250 (very strong, C-B str.), 1150 (strong, C-O str.), 1030 (medium, C-O str.); δ_H (300 MHz) 1.29 (12H, s, 4xCH_3), 5.86 (1H, dd, *J* 19.2, 13.8Hz, -**CH**:B), 6.03 (1H, bdd, *J* 13.3, 4.36Hz, :**CH**), 6.16 (1H, dd, *J* 19.2, 4.36Hz, :**CH**); δ_C (75.5 MHz) 25.1

(-CH_3), 83.7 (Cq, -CO-), 135.3 (b, :CHB), 137.4 (H_2C:); *m/z* (FAB$^+$) 136 (100%); (CI$^+$) 172.0525 (100%, M+NH_4^+, $C_8H_{19}BNO_2^+$ requires 172.0522)

1-Phenyl-3-butyn-1-ol 219[135, 124]



Method A

Propargyl bromide (8.8 mL of an 80% solution in toluene, 84.0 mmol), benzaldehyde (5.69mL, 56.0mmol), tetra-*n*-butyl ammonium bromide (18.1 g, 56.0 mmol) and tin(II) chloride (20.9 g, 92.0 mmol) were added to 170 mL of distilled water, and the resulting mixture stirred at 50 °C for 8 hours. The mixture was cooled and extracted with diethyl ether, and the aqueous phase washed with diethyl ether (3 x 20 mL). The combined organic phases were washed with distilled water, dried ($MgSO_4$) and concentrated to give mostly **219** as a pale yellow oil; purification by Kugelrohr distillation gave pure **219** (9.41 g, 67%) ν_{max}(film)/cm^{-1} 3420 (b, alcohol O-H str), 3300 (medium, alkyne C-H str.), 3030 (weak, aryl C-H str.), 2920 (weak, aliphatic C-H str.), 2140 (weak, C≡C str.), 1600, 1510 (medium, C=C aromatic str.), 1450 (medium, aliphatic C-H def.), 1050 (b, medium, C-O str.); δ_H (300 MHz) 2.10 (1H, s, *J* 2.7, ≡C**H**), 2.69 (2H, dd, *J* 6.5, 2.7, -C**H**$_2$-), 4.80 (1H, t, *J* 6.5, -C**H**-); 7.32-7.65 (5H, m, Ar**H**); δ_C (75.5 MHz) 29.8 (-CH_2-), 71.4 (-CH(OH)), 72.7 (≡CH), 81.2 (-C≡CH), 127.4 (Ar-C), 128.4 (Ar-C), 129.5 (Ar-C), 143.0 (Ar-C) *m/z* (CI$^+$) 164.2233 (100%, M+NH_4^+, $C_{10}H_{14}NO^+$ requires 164.2237)

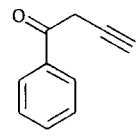
Method B

Aluminium powder (1.95 g, 73.0 mmol) and mercuric chloride (259 mg, 1.0 mmol) were added in one portion to a solution of propargyl bromide (7.18 mL of an 80% solution in toluene, 66.0 mmol) in anhydrous diethyl ether stirred under argon at room temperature. The mixture was warmed to inititiate the reaction (signified by effervecsence and the solution becoming almost black). The solution was refluxed for 1 hour, then cooled to -78 °C. Benzaldehyde (7.38 mL, 73.0 mmol) was added dropwise over an hour. The solution was maintained at -78 °C for a further 2 hours, before being refluxed for a further 1 hour. After this time, the reaction was quenched with saturated NH_4Cl and diluted with Et_2O. The organic phase was separated and washed with brine and distilled water; concentration of the combined organic layers after drying ($MgSO_4$) gave crude **219** as a dark red oil (60%); analytical data was consistent with product obtained by method A.

Method C

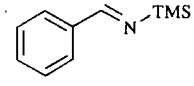
A mixture of benzaldehyde (9.58 mL, 94.0 mmol), propargyl bromide (8.97 mL of an 80% solution in toluene, 85.0 mmol) in anhydrous diethyl ether was added to a mixture containing activated zinc dust (7.00 g, 100.0 mmol) and mercuric chloride (50 mg) in dry toluene. The mixture was maintained at gentle reflux for 3 hours; after this time, the reaction was cooled and extracted into diethyl ether (100 mL) and washed with water (3 x 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil containing **219** (55%); analytical data was consistent with product obtained by method A.

1-Phenyl-3-butyn-1-one 221a[129]



To a solution of **221a** (2.5 g, 17.0 mmol) in acetone (14 ml) cooled to -10 °C was added a solution containing sodium dichromate dihydrate (1.3 g, 4.0 mmol) and concentrated H_2SO_4 (1.2 mL) in water (1.2 mL) dropwise with stirring. The reaction temperature was maintained below -5 °C during the addition. The reaction was then allowed to warm to room temperature, and was stirred for a further 10 minutes. After this time the mixture was diluted with diethyl ether, and filtered. The filtrate was washed with saturated sodium carbonate solution, and the organic phase separated and washed with distilled water. Drying ($MgSO_4$) and concentration gave a dark red oil containing **221a** (less than 10%) data for crude product ν_{max} (film)/cm^{-1} 3340 (weak, alkyne C-H str.), 3240 (weak, aryl C-H str.), 2105 (weak, C≡C str.), 1690 (strong, C=O str.), 1600, 1550 (medium, Ar-H str.); δ_H (300 MHz) 2.33 (1H, t, *J* 2.6Hz, -C**H**$_2$-), 3.89 (2H, d, *J* 2.6Hz, -CH-), 7.25-7.65 (3H, m, Ar**H**), 7.85-8.20 (2H, m, Ar**H**); δ_C (75.5 MHz) 30.9 (-**C**H$_2$-), 74.1 (-C≡**C**H), 83.3 (-**C**≡CH), 127.7 (Ar-**C**), 129.1 (Ar-**C**), 130.6 (Ar-**C**), 134.1 (Ar-**C**), 193.1 (Cq, **C**=O) *m/z* (CI+) 162 ($M+NH_4^+$, 60%).

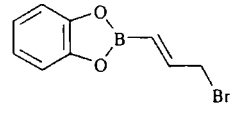
***N*-[(E)-Phenylmethylidene]-*N*-(trimethylsilyl)amine 222**[133]



To HMDS (10.8 mL, 51.8 mmol) cooled to 0 °C and stirred under argon was added *n*-BuLi 18.8 mL of a 2.5 M solution, 47.0 mmol) dropwise. The solution was stirred for 30mins, and the solvent removed until a white ppte was formed. The ppte was cooled to 0°C, and benzaldehyde (4.8 mL, 47.0 mmol) added over 10 mins. The reaction was stirred for 30 mins, and allowed to warm to room temperature. Product was purified by

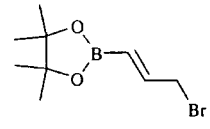
vacuum distillation (Kugelrohr, 110-115 °C, 0.8 mmHg), affording **222** as a pale yellow oil (5.58 g, 69%); analytical data matched that reported in the literature; δ_C (75.5 MHz) 0.4 (-Si**Me**$_3$), 127.6 (Ar-**C**), 128.3 (Ar-**C**), 131.7 (Ar-**C**), 140.0 (Ar-**C**), 169.4 (-**C**=N) *m/z* (ES^+) 178.1048 (MH^+, 100%, $C_{10}H_{16}NSi$ requires 178.1052).

2-[(*E*)-3-Bromo-1-propenyl]-1,3,2-benzodioxaborole 223a[225]



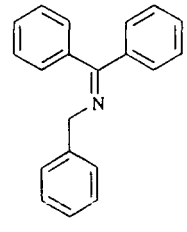
Propargyl bromide (0.88mL of an 80% solution in toluene, 8.3mmol) was cooled to 0°C under argon, and catecholborane (0.88mL, 8.3mmol) carefully added with stirring. The reaction mixture was heated to 50°C for 1h. The resulting mixture containing mostly **223a** (90%) was used without further purification. δ_H (300 MHz) 4.15 (2H, d, *J* 8.3Hz, -CH_2-), 6.07 (1H, d, *J* 17.7Hz, :C**H**-B), 7.15 (2H, m, ArH), 7.27 (1H, m, ArH), 7.40 (1H, m, H_2C-C**H**:); δ_C (75.5 MHz) 33.5 (-CH_2-), 113.1 (Ar-C), 123.4 (Ar-C), 129.5 (C:CH-B), 138.3 (CH_2C:), 149.8 (Ar**C**-O).

2-[(*E*)-3-Bromo-1-propenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 223b[226]



Pinacolborane (0.158 mL, 1.1 mmol) was added to a stirred solution of $Rh(PPh_3)_3Cl$ (9.25 mg, 0.01 mmol) in dry DCM (1 mL) at 25 °C under argon. The solution was stirred for 2 minutes, and propargyl bromide (0.104 mL of 80% solution in toluene, 1 mmol) added. After stirring for 3 hours, the reaction was quenched with water (1 mL) and extracted into diethyl ether (1 mL). Drying ($MgSO_4$) and concentration of the organic phase gave a yellow oil containing **223b** (58%, 62% internal isomer **223c**); analytical data was consistent with reported literature values.

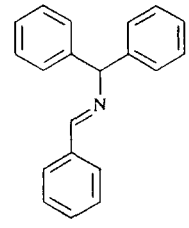
***N*-(Diphenylmethylene)(phenyl)methanamine 247**[159]



A solution of benzophenone imine (5mL, 25.5 mmol) and benzylamine hydrochloride (3.7 g, 25.5 mmol) in dry DCM (25 mL) were stirred for 24h under argon at room temperature. The crude mixture was filtered, and the filtrate concentrated *in vacuo* to give the crude product as a pale yellow solid (6.81 g, 98%). Recrystallization from

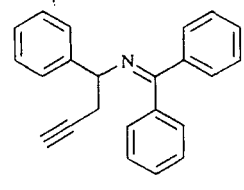
pentane gave pure **247** as a white crystalline solid (6.57 g, 95%); m.p. 57-59°C, lit. value 54-56°C;[227] ν_{max}(film)/cm^{-1} 1630 (strong, C=N str.); δ_H (300 MHz) 4.68 (2H, s, -CH_2-), 7.30-7.85 (15H, m, ArH); δ_C (75.5 MHz) 57.9 (-CH_2-), 127.0 (ArC), 128.2 (ArC), 128.5 (ArC), 128.8 (ArC), 130.7 (ArC), 137.1 (Cq, ArC), 140.2 (Cq, ArC), 141.1 (Cq, ArC), 169.2 (Cq, C=N); *m/z* (ES$^+$) 272.1436 (100%, MH$^+$, $C_{20}H_{18}N^+$ requires 272.1439).

Diphenyl-*N*-[(*E*)-phenylmethylidene]methanamine 248[159]



To a stirred solution of diphenylmethanamine (3.1 g, 16.9 mmol) in dry DCM (25 mL) under argon at room temperature was added anhydrous $MgSO_4$ (4 g) and benzaldehyde (1.74 g, 16.4 mmol) portionwise. The reaction was stirred until TLC indicated consumption of benzaldehyde (5h), after which the crude mixture was concentrated *in vacuo* to give **248** as a pale yellow solid (4.25 g, 93%). Recrystallization from pentane gave pure **248** (4.19 g, 91%) as a pale yellow crystalline solid; m.p. 100-103°C, lit. value 98-100°C;[159] ν_{max}(film)/cm^{-1} 1638 (strong, C=N str.); δ_H (300 MHz) 5.65 (1H, s, -CH), 7.22-7.63 (13H, m, ArH), 7.9 (2H, m, ArH), 8.45 (1H, s, :NH); δ_C (75.5 MHz) 77.9 (Ph_2CH-), 127.3 (ArC), 127.7 (ArC), 128.9 (ArC), 129.0 (ArC), 130.5 (ArC), 131.2 (ArC), 136.8 (Cq, ArC), 144.4 (Cq, ArC), 161.2 (-C=N); *m/z* (ES$^+$) 272.3651 (100%, MH$^+$, $C_{20}H_{18}N^+$ requires 272.3652).

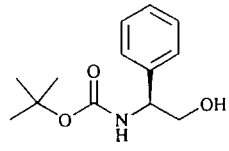
***N*-(Diphenylmethylene)-1-phenyl-3-butyn-1-amine 249**



To diphenyl-*N*-[(*E*)-phenylmethylidene]methanamine (2.00 g, 7.4 mmol) in anhydrous THF (20mL) was added potassium *t*-butoxide (1.00 g in 10 mL of THF, 1.2 eq). Propargyl bromide (1.00 g, 1.1 eq) was then added to the purple solution, and the reaction stirred under argon at room temperature. After 2h, the reaction was quenched with cold water and extracted with DCM (2 x 20 mL). Drying over $MgSO_4$ and concentration *in vacuo* of the combined organic layers gave an orange liquid; purification by flash chromatography (2:1 pet. ether/DCM as eluant) gave propargylimine **249** as the minor fraction; colourless solid (0.19 g, 17%) ν_{max}(film)/cm^{-1}

3295 (strong, C-H str. alkyne), 2123 (weak, C≡C str.), 1637 (medium, C=N str.); δ_H (300 MHz) 1.97 (1H, t, *J* 3.1Hz, C≡C**H**), 2.71-2.77 (1H, m, -C**H**$_2$-), 2.83-2.89 (1H, m, -C**H**$_2$-), 4.63-4.66 (1H, m, -C**H**), 7.15-7.75 (15H, m, Ar**H**); δ_C (75.5 MHz) 27.6 (-**C**H$_2$C≡CH), 63.9 (PhCH-), 75.1 (≡**C**H), 84.1 (q, HC≡**C**-), 127.4 (Ar**C**), 127.6 (Ar**C**), 128.5 (Ar**C**), 128.8 (Ar**C**), 129.3 (Ar**C**), 129.9 (Ar**C**), 137.2 (Cq, Ar**C**), 137.3 (Cq, Ar**C**), 141.9 (Cq, Ar**C**), 170.1 (Cq, **C**=N); *m/z* (FAB$^+$) 309.4146 (100%, MH$^+$, $C_{23}H_{20}N^+$ requires 309.4149). major fraction was found to be *N*-(diphenylmethylene)-*N*-{2-[(diphenylmethylene)amino]-1,2-diphenylethyl}amine **255** (2.71g, 68%), structure determined by XRD.

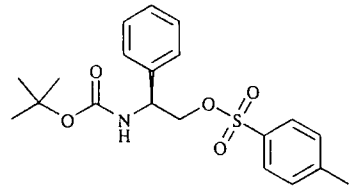
***tert*-Butyl (1*S*)-2-hydroxy-1-phenylethylcarbamate 257**[161]



To a suspension of $NaBH_4$ (15.0 g, 0.396 mol) in dry THF (350 mL) cooled to 0 °C and stirred under argon was added I_2 (42.0 g, 0.165 mol) as a solution in dry THF (75 mL) dropwise over 1h. When evolution of gas ceased, (*S*)-phenylglycine **256** (25.0 g, 0.165 mol) was added portionwise over 1h, the reaction was then refluxed for 18h. After this time, the reaction was cooled to 0 °C and MeOH (30·mL) added cautiously and the mixture stirred. After evolution of gas ceased (20 minutes), THF (200 mL) was added to the clear solution, and the reaction was cooled to 0 °C. Et_3N (24.2 mL, 0.165 mol) was added, followed by di-*tert* butyl dicarbonate (38.0 g, 0.167 mol) portionwise with vigorous stirring; the reaction was then warmed to room temperature and stirred for 3h. Solvent was removed *in vacuo,* and the white residue was stirred with EtOAc (200mL) and water (150 mL). The white residues were destroyed by the additon of 1:1 brine / 10% HCl (200 mL). After stirring for 10 minutes, the mixture was then poured into a separating funnel containing EtOAc (150 mL), and the phases separated. The aqueous phase was washed with EtOAc (2 x 100 mL), and the combined organic phase then washed with a) 1:1 solution of brine / 5% HCl (2 x 100 mL) b) 1:1 solution of sat. $NaHCO_3$ solution and brine (2 x 100 mL), and finally with H_2O to pH 7. After drying over $MgSO_4$, solvents were partially removed *in vacuo* to leave approximately 50mL of mother liquor; to this was added hexane (150 mL). After chilling at -10 °C for 12h, the white crystals were collected to afford a crude white solid that was recrystallized (3 crops) from cold DCM-cyclohexane; reconcentration and flash chromatography (Si gel, 1:1 Et_2O-hexane) gave a further 2 g of pure material; total recovery of pure **257** (37.6 g, 96%) as white needles; m.p. 136-138°C (from cyclohexane/DCM), lit. value 137-

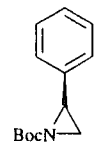
138°C;[161] $[\alpha]^{21}_D$= +39.8 (*c* 1.6, $CHCl_3$) lit. $[\alpha]^{22}_D$= +39.4 (*c* 1.67, $CHCl_3$);[161] $C_{13}H_{19}O_3N$ requires C 65.8 H 8.07 N 5.90%; found C 66.1 H 8.78 N 6.01%; ν_{max} (film)/cm^{-1} 3525 (broad, O-H str.), (003430-2980 (several bands, broad, strong, N-H amide and Ar-H str.), 1680 (strong, C=O str, amide), 1551 (medium, N-H bend), 1366 ((strong, -$C(CH_3)_3$ C-H str.), 1060 (medium, C-O str.); δ_H (300 MHz) 1.39 (9H, s, 3xCH_3), 3.50 (1H, bs, -CH_2OH, *exchanges with* D_2O), 3.90 (2H, d, *J* 4.5Hz, -CH_2-), 4.75 (1H, bs), 5.26 (1H, bs), 7.25-7.41 (5H, m, ArH); δ_C (75.5 MHz) 28.6 (-CH_3), 57.9 (-COH), 66.2 (CHPh), 78.5 (Cq, $C(CH_3)_3$), 127.0 (ArC), 128.3 (ArC), 128.7 (ArC), 142.2 (Cq, ArC), 155.5 (Cq, -C=O); *m/z* (ES^+) 238.3018 (100%, MH^+, $C_{13}H_{20}O_3N^+$ requires 238.3020), 220, 206, 199, 182, 168, 150, 138, 124, 106, 91, 57.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl 4-methylbenzenesulfonate 258[169]



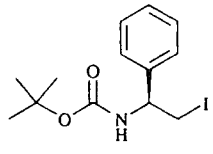
To a solution of amino alcohol **257** (10.0 g, 0.0421 mol) dissolved in freshly distilled DCM (150 mL), stirred under Ar and cooled to 0 °C, was added freshly distilled Et_3N (8.85 mL, 1.5 eq) followed by, over 1h, tosyl chloride (8.03 g, 1eq) as a solution in DCM (50 mL). The solution was allowed to stir at < 20 °C for 16h, before a sat. solution of $NaHCO_3$ (75 mL) was added. After stirring for 5 minutes, the phases were separated and the aqueous phase washed with DCM (50 mL). The combined organic phases were washed with brine (2 x 50 mL) and dried over $MgSO_4$. Removal of solvents *in vacuo* (Et_3N and DCM) gave a cream solid (14.3 g, 87%) that was recrystallized from DCM-hexane to afford tosylate **258** as a cream voluminous powder (13.8 g, 82%); m.p. 164-166°C, lit value 160°C;[169] $[\alpha]^{20}_D$= +2.5 (*c* 3, $CHCl_3$) lit. value for (R) enantiomer $[\alpha]^{25}_D$= -2 (*c* 3, $CHCl_3$);[169] ν_{max} (KBr disc)/cm^{-1} 3495-2975 (several bands, strong, N-H amide and Ar-H str.), 1675 (strong, C=O str, amide), 1555 (medium, N-H bend), 1395 (weak, SO_2-O str.), 1365 ((strong, -$C(CH_3)_3$ C-H str.), 1060 (C-O str.); δ_H (400 MHz) 1.45 (s, 9H, 3xCH_3); 2.44 (s, 3H, ArCH_3), 4.22 (m, 2H, -CH_2-), 4.91 (bs, 1H, PhCH), 5.23 (bs, 1H, -NH, *exchanges with* D_2O), 7.20 (d, 2H, *J* 8Hz, ArH), 7.30 (m, 5H, ArH), 7.65 (d, 2H, *J* 8Hz, ArH); δ_C (100 MHz) 22.1 (PhCH_3), 28.7 ($C(CH_3)_3$), 55.0 (-CH_2-), 71.9 (PhCH), 80.5 (Cq, $C(CH_3)_3$), 127.0 (ArC), 129.1 (ArC), 128.4 (ArC), 130.3 (ArC), 132.8 (Cq, ArC), 138.2 (Cq, ArC), 145.4 (Cq, ArC), 155.3 (Cq, C=O), *m/z* (ES^+) 392.4966 (100%, MH^+, $C_{20}H_{27}NO_5S^+$ requires 392.4970).

***tert*-Butyl (2*R*)-2-phenyl-1-aziridinecarboxylate 259**[180]



To a solution of **257** (1.0 g, 4.20 mmol) and *p*-toluenesulfonyl chloride (0.96 g, 5.00 mmol) in dry Et_2O (100 mL) stirred at room temperature under argon was added freshly powdered anhydrous KOH (0.95g, 16.9mmol). After refluxing for 4h, the mixture was poured into a separating funnel containing crushed ice, and the organic phase separated, washed with brine (50 mL) and dried over $MgSO_4$. After removing the solvent *in vacuo*, the pale yellow liquid was purified by column chromatography (silica gel, 1:1 hexane / Et_2O as eluant) to give **259** as a white waxy solid (0.81 g, 87%) that was best stored at -20°C under argon. $[\alpha]^{21}_D$= -165.2 (*c* 1, DCM) lit. $[\alpha]^{20}_D$= -163.5 (*c* 1, DCM);[180] ν_{max} (film)/cm^{-1} 3555-2997 (several bands, strong, N-H amide and Ar-H str), 1678 (strong, C=O str, amide), 1368 (strong, -C(CH$_3$)$_3$ C-H str.); δ_H (400 MHz) 1.48 (9H, s, 3x-C**H**$_3$), 2.31 (1H, d, *J* 5Hz, -C**H**$_2$-), 2.64 (1H, d, *J* 5Hz, -C**H**$_2$-), 3.42 (1H, t, *J* 5Hz, -C**H**-), 7.15-7.48 (5H, m, Ar**H**); δ_C (75.5 MHz) 28.1 (-C(**C**H$_3$)$_3$), 32.8 (-**C**H$_2$-), 46.4 (-**C**HPh), 79.8 (Cq, -**C**(CH$_3$)$_3$), 122.4 (Ar**C**), 127.5 (Ar**C**), 128.9 (Ar**C**), 144.4 (Cq, Ar**C**), 154.1 (Cq, **C**=O); *m/z* (ES$^+$) 219.2788 (100%, $C_{13}H_{18}NO_2^+$ requires 219.2789).

***tert*-Butyl (1*S*)-2-iodo-1-phenylethylcarbamate 260**[161]



To a stirred solution of tosylate **258** (1.00 g, 2.6 mmol) in anhydrous propionitrile (15mL) was added sodium iodide (0.80 g, 5.1 mmol). The mixture was stirred at room temperature for 2 days, then diluted with diethyl ether. The reaction was filtered through Celite, evaporated, and the residue redissolved in DCM. After washing with saturated $Na_2S_2O_3$ solution (30 mL) and water (50 mL), the organic phase was dried ($MgSO_4$) and concentrated to give a cream solid that was recrystallized from acetone-water to give crude **260** as a white solid; purification by column chromatography (silica gel, 1:1 hexane / Et_2O as eluant) afforded an analytically pure sample (0.76 g, 88%) as fine white crystals; m.p. 97-99°C, lit. value 97-98°C;[161b] $[\alpha]^{20}_D$= +50.9 (*c* 0.9, $CHCl_3$) lit.$[\alpha]^{25}_D$= +51.6 (*c* 0.88, $CHCl_3$);[161] $C_{13}H_{18}NO_2I$ requires C 44.97 H 5.22 N 4.03%; found C 45.11 H 5.01 N 3.89%; ν_{max}(KBr disc)/cm^{-1} 3347-2920 (several bands, strong, N-H amide and Ar-H str.), 1689 (strong, C=O str. amide), 1556 (medium, N-H bend.), 1370 (strong, -C(CH$_3$)$_3$ C-H str.), 515 (medium, C-I str.); δ_H (400 MHz) 1.45 (9H, s,

3x(CH_3)), 3.42-3.60 (2H, m, -CH_2-), 4.7 (1H, m, -CH-), 5.10 (1H, bs, -NH), 7.25-7.42 (5H, m, ArH); δ_C (100 MHz) 28.7 (-C(CH_3)$_3$), 55.3 (-CI), 72.9 (CHPh), 80.5 (Cq, -C(CH_3)$_3$), 126.5 (ArC), 128.5 (ArC), 129.3 (ArC), 140.5 (Cq, ArC), 155.3 (Cq, C=O) *m/z* (ES^+) 348.0463 (100%, MH^+, $C_{13}H_{19}NO_2I^+$ requires 348.0460).

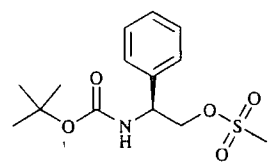
tert-Butyl (1*S*)-2-iodo-1-phenylethylcarbamate 260 from 257 method A:

To a stirred solution of polystyryl diphenylphosphine (1.18 g, 3.16 mmol) in dry DCM (15 mL) at RT under Ar was added I_2 (0.40 g, 3.16 mmol). After stirring for 15 mins., imidazole (0.24 g, 3.59 mmol) was added, and the mixture was stirred for a further 15 mins. **257** (0.34 g, 1.44 mmol) was added as a solution in DCM (5 mL), and the resulting mixture refluxed for 2h. After this time, the reaction was filtered through Celite (washing with DCM), and the organic phase washed with $Na_2S_2O_3$, and then with water to pH 7. Concentration *in vacuo* gave 0.45 g of pure **260** as a white solid (91%).

tert-Butyl (1*S*)-2-iodo-1-phenylethylcarbamate 260 from 257 method B:

To a stirred solution of PPh_3 (2.42 g, 2.2 eq.) in dry DCM (15 mL) at RT under Ar was added I_2 (1.17 g, 2.2 eq). After 35 mins., imidazole (0.71 g, 2.5 eq.) was added, and the solution stirred for a further 15 mins. **257** (1.00 g, 4.20 mmol) in DCM (5 mL) was added in one portion, and the resulting solution refluxed for 6h. The reaction was cooled, and the organic phase washed with $Na_2S_2O_3$ (2 x 10 mL), water (2 x 20 mL), and dried over $MgSO_4$. Silica gel chromatography of the concentrated material (gradient elution from pet ether 60-80 to 8:1 pet. ether / EtOAc) afforded 0.98 g of **260** (67%).

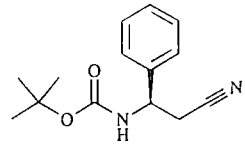
(2*S*)-2-[(_tert_-Butoxycarbonyl)amino]-2-phenylethyl methanesulfonate 262[171e]



To a solution of **257** (10.0 g, 42.0 mmol) in freshly distilled DCM (150 mL), cooled to 0 °C and stirred under argon, was added freshly distilled Et_3N (8.90mL, 1.5 eq.), followed by, over 1h, a solution of freshly distilled methanesulfonyl chloride (3.43 mL, 1.05 eq.) in dry DCM (50 mL). The solution was stirred at RT for 12h, then sat. $NaHCO_3$ (75 mL) was added and the phases were separated after stirring for 10 min. The aqueous phase was washed with DCM (2 x 25mL), and the combined organic phases were washed with sat. NaCl (2 x 50mL) and dried over $MgSO_4$. Concentration *in vacuo* (to remove Et_3N and DCM) gave an off-white solid (13.9 g) that was recrystallized from DCM / hexane to give cream crystals of **262** (11.5 g, 87%); m.p. 115-117°C, lit. value 112-114°C;[171e] $[\alpha]^{22}_D$= +23.1 (*c* 0.9, $CHCl_3$) lit. val for (*R*) enantiomer $[\alpha]^{25}_D$= -21 (*c* 1, $CHCl_3$);[171f] $C_{14}H_{21}NO_5S$ requires C 53.32 H 6.71 N 4.44%; found C 53.11 H 6.67 N

4.34%; ν_{max}(KBr disc)/cm^{-1} 3445-2979 (several bands, strong, N-H amide, and Ar-H str.), 1668 (strong, C=O str, amide), 1558 (medium, N-H bend), 1389 (weak, SO_2-O str.), 1367 (strong, -C(CH_3)$_3$ C-H str.), 1063 (medium, C-O str.); δ_H (500 MHz) 1.4 (9H, bs, 3xCH_3), 2.84 (3H, s, -CH_3), 4.39 (2H, s, -CH_2-), 4.99 (1H, bs, -CHPh), 5.33 (1H, bs, NH, *exchanges with D_2O*); δ_C (125.5 MHz) 28.3 (-C(CH_3)$_3$), 37.9 (-CH_3), 53.3 (CHPh), 71.4 (-$CH_2OSO_2CH_3$), 81.1 (Cq , b, C(CH_3)$_3$,), 127.5 (ArC), 128.9 (ArC), 129.9 (ArC), 139.8 (Cq, ArC), 155.8 (Cq, C=O); *m/z* (ES$^+$) 338.1 (100%, (M+Na)$^+$).

<u>*tert*-Butyl (1*R*)-2-cyano-1-phenylethylcarbamate 263 from 261</u>[161b]



A solution of tosylate **258** (5.0 g, 12.8 mmol) in DMF (10 mL) was slowly added to a stirred solution of NaCN (1.9 g, 39.0 mmol) in DMF (20 mL) under argon. The reaction was stirred for 24h at room temperature, then diluted with H_2O (50 mL) and extracted into ethyl acetate (50 mL). The organic phase was washed with H_2O (3 x 20mL), 5% HCl (3 x 20mL) and finally H_2O (50 mL), before being dried over $MgSO_4$ and concentrated *in vacuo* to give crude **263** as a cream solid. Recrystallization from DCM-hexane gave pure **263** as a white solid (3.03 g, 96%); m.p. 110-112°C, lit. value 112-113°C;[161b] $[\alpha]^{23}_D$= +41.6 (*c* 0.5, EtOH) lit. $[\alpha]^{25}_D$= +42.2 (*c* 0.45, EtOH);[161b] $C_{14}H_{18}N_2O_2$ requires C 68.26, H 7.36, 11.37%; found C 68.07, H 7.29, N 11.49%; ν_{max}(KBr disc)/cm^{-1} 3440-2948 (several bands, strong, N-H str. and Ar-H str.), 2250 (weak, C≡N str.), 1688 (strong, C=O str.), 1555 (medium, N-H bend.), 1367 (strong, -C(CH_3)$_3$ C-H str.); δ_H (500 MHz) 1.46 (9H, s, 3xC(CH_3)$_3$), 2.88 (1H, dd, *J* 16.4Hz, 6.2Hz, -CH_2-) 3.00 (1H, dd, *J* 16.4, 6.2Hz, -CH_2-), 4.90-5.07 (1H, m, -CHPh-), 5.18 (1H, bd, *J* 5.7Hz, -NH *exchanges with D_2O*), 7.33-7.44 (5H, m, ArH); δ_C (100 MHz) 25.6 (-CH_2-), 28.7 (-C(CH_3)$_3$), 51.6 (-CHPh), 80.9 (Cq, -C(CH_3)$_3$), 117.53 (Cq, -C≡N), 126.6 (ArC), 128.9 (ArC), 129.5 (ArC), 139.1 (Cq, ArC), 155.3 (Cq, C=O); *m/z* (ES$^+$) 247.1446 (100%, MH$^+$, $C_{14}H_{19}N_2O_2^+$ requires 247.1446);

<u>*tert*-Butyl (1*R*)-2-cyano-1-phenylethylcarbamate 263 from 262</u>

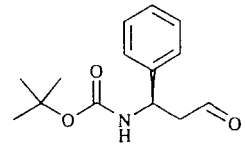
To a solution of mesylate **262** (10 g, 31.7 mmol) in anhydrous DMSO (150 mL) stirred under argon, was added NaCN (4.7 g, 3 eq.) in one portion. The suspension was stirred vigorously at 45 °C for 18h, then cooled to 0 °C. Water (250 mL) was added, and the DMSO / H_2O phase was washed with Et_2O (3 x 100mL). The combined ether extracts were washed with sat. NaCl (3 x 100mL), and dried over $MgSO_4$. Concentration *in*

vacuo gave a white solid that was recrystallized from cold DCM / hexane to give white crystals of **263** (5.84 g, 74%).

***tert*-Butyl (1*R*)-2-cyano-1-phenylethylcarbamate 263 from 258: alternative procedure**

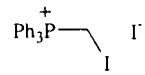
The conditions above were followed, substituting the N-Boc amino mesylate **262** for the corresponding tosylate **258**. Yield is typically 70%.

***tert*-Butyl (1*R*)-3-oxo-1-phenylpropylcarbamate 264**[181]



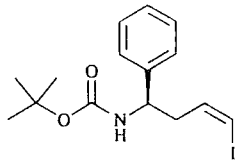
To a partially solubilized solution of nitrile **263** (5.00 g, 20.3 mmol) in dry Et_2O (100 mL) cooled to –40°C and stirred vigorously under argon was added DIBAL-H (81.2 mL of a 1M solution in PhMe, 4 eq) over 15 minutes. The reaction was stirred for a further 0.5h, then quenched by the cautious addition of MeOH (5 mL). The mixture was immediately poured into a separatory funnel containing saturated NH_4Cl solution (100 mL). After warming to room temperature, the thick gel was progressively destroyed by the slow addition of 0.1M HCl, then 1M HCl, and finally the pH was reduced to 2-3 by the addition of 3M HCl. After extracting with EtOAc (100 mL), the organic phase was washed with i) 2 x 50mL of a 1M HCl / brine solution (1:1) ii) 2 x 50mL of a saturated $NaHCO_3$ / brine solution (1:1). The organic phase was dried (K_2CO_3) and concentrated *in vacuo*. The resulting yellow residue was distilled (Kugelrohr, 0.05 mmHg) to give a white solid that was recrystallized from 1:4 diisopropyl ether / hexane; recovered 3.59 g (71%); m.p. 92-93°C, lit. value 91-93°C;[181] $[\alpha]^{23}_D$= +29.9 (*c* 1.5, $CHCl_3$) lit. value for (*S*) enantiomer: $[\alpha]^{25}_D$= -30.1 (*c* 1.5, $CHCl_3$);[181] $C_{14}H_{19}NO_3$ requires C 67.45 H 7.68 N 5.62%; found C 67.41 H 7.61 N 5.46%; ν_{max}(KBr disc)/cm^{-1} 3440-2942 (several bands, strong, N-H str. and Ar-H str.), 2722 (weak, C-H str. aldehyde), 1742 (strong, C=O str. aldehyde), 1678 (strong, C=O str. amide), 1553 (medium, N-H bend.), 1374 (strong, -$C(CH_3)_3$ C-H str.); δ_H (300 MHz) 1.41 (9H, s, 3x$C(CH_3)_3$), 2.90-3.11(2H, m, -CH_2-), 5.01-5.23 (2H, m, -CHPh+NH), 7.23-7.39 (5H, m, ArH), 9.73 (1H, s, CHO); δ_C (100 MHz) 28.2 (-$C(CH_3)_3$), 50.1 (-CHPh), 80.1 (Cq, b, ($CH(CH_3)_3$), 126.2 (ArC), 128.3 (ArC). 129.4 (ArC). 141.5 (Cq, ArC), 154.5 (Cq, C=O), 200.4 (Cq, CHO); *m/z* (ES^+) 272.3 (100%, $(M+Na)^+$).

(Iodomethyl)triphenylphosphonium iodide 265[228]



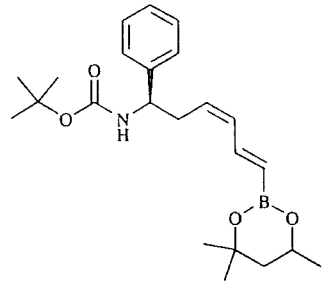
To a solution of triphenylphosphine (10.0 g, 38.1 mmol) in dry DCM (100 mL) was added diidomethane (12.3 mL, 4 eq). The solution was stirred at RT for 18h, and after this time the mixture was concentrated *in vacuo* (0.05 mmHg). Hexane was added to the resulting semi-sold material, and the solution was filtered. The solids were washed with hexane, and dried *in vacuo*. Obtained **265** as a cream solid that was best stored under argon (18.9 g, 94%); δ_H (500MHz) 5.01 (2H, d, *J* 13.8Hz, -C**H**$_2$-), 7.72-7.94 (15H, m, Ar**H**); *m/z* (ES$^+$ in 1% TFA / MeCN) 403.1 (100%, (M-I)$^+$)

<u>*tert*-Butyl (1*R*,3*Z*)-4-iodo-1-phenyl-3-butenylcarbamate 266</u>[184]



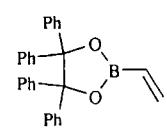
To a slurry containing (iodomethyl)triphenylphosphonium iodide **265** (2.46 g, 1.1 eq) in dry THF (50 mL) was added KHMDS (18.0 mL of a 0.5M sol. in PhMe, 2.2 eq.) dropwise. The orange-black suspension was stirred for 10min, and cooled to –78°C before adding HMPA (2.80 mL, 4 eq.). After 15min, a solution of aldehyde **264** (1.00 g, 4.0 mmol) in dry THF (15 mL) was added. After stirring for 15min, the reaction was quenched with sat. NH_4Cl, and filtered *in vacuo*. The resulting solution was extracted with Et_2O (2 x 25mL), and the organic phase was washed with brine, and dried over $MgSO_4$. Removal of solvents gave a dark brown oil that was subjected to column chromatography (Si gel, eluted with hexane, then 8:1 hexane / EtOAc). Obtained pure **266** (0.695 g, 47%) as an off-white solid (>10:1 *Z*/*E*; isomers could not be separated); m.p. 105-107°C, lit. value 104-106°C;[184] $[\alpha]^{25}_D$= +27.9 (*c* 1.20, $CHCl_3$) lit. val for (*S*) enantiomer $[\alpha]_D$= -26.5 (*c* 1.19, $CHCl_3$);[184] ν_{max}(KBr disk)/cm^{-1} 3380-2977 (several bands, strong, N-H str. and Ar-H str.), 1688 (strong, C=O str.), 1610 (medium, C=C str.), 1560 (medium, N-H bend); δ_H (400 MHz) 1.42 (9H, bs, 3xC(C**H**$_3$)$_3$), 2.63 (2H, m, -C**H**$_2$-), 4.86 (2H, m, C**H**Ph + N**H**), 6.13-6.17 (1H, dd, *J* 16.4, 9.3Hz, :C**H**), 6.35 (1H, d, *J* 9.3Hz, :C**H**), 7.26-7.35 (5H, m, Ar**H**); δ_C (100 MHz) 28.3 (-C(**C**H$_3$)$_3$), 40.9 (-**C**H$_2$-), 53.9 (-**C**HPh), 80.2 (Cq, b, -**C**(CH$_3$)$_3$), 85.8 (:**C**HI), 126.4 (Ar**C**), 127.8 (Ar**C**), 129.1 (Ar**C**), 137.8 (:**C**H), 142.0 (Cq, Ar**C**), 156.8 (Cq, **C**=O); *m/z* (ES$^+$) 374.2361 (100%, $C_{15}H_{21}INO_2^+$ requires 374.2364)

tert-Butyl-(1*R*,3*Z*,5*E*)-1-phenyl-6-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)-3,5-hexadienylcarbamate 268



Palladium acetate (6 mg, 0.0267 mmol), triphenylphosphine (15 mg, 0.0572 mmol) and iodide **266** (100 mg, 0.268 mmol) were suspended in freshly distilled toluene (5 mL). Vinylboronate **272** (60 μL, 0.348 mmol) and tri-*n*-butylamine (76 μL, 0.322 mmmol) were added, and the mixture was degassed thoroughly (freeze-pump-thaw). The reaction was heated to 120 °C in a sealed tube for 20h. The mixture was filtered through Celite, extracted into Et_2O (2 x 5mL) and washed with 5% HCl (2 x 5mL) and brine (5 mL). The combined organic phases were dried over $MgSO_4$ and solvents removed *in vacuo*. Purification by column chromatography (Si gel, 10:1 hexane / ethyl acetate as eluant) gave the desired compound **268** as a 19:1 mixture with the Suzuki product (75 mg, 70%); yellow oil; ν_{max}(film)/cm^{-1} 3440-2960 (several bands, strong, N-H str. and Ar-H str.), 1685 (strong, C=O str.), 1620 (medium, C=C str.), 1604 (medium, C=C str.), 1557 (medium, N-H bend); δ_H (500 MHz) 1.21 (3H, s, -C**H**$_3$), 1.23 (9H, s, -C(C**H**$_3$)$_3$), 1.27 (6H, s, 2 x -C**H**$_3$), 1.38 (1H, m, -C**H**), 1.69 (1H, m, -C**H**), 2.82 (2H, dd, *J* 14.6, 6.91Hz, -C**H**$_2$), 4.12 (1H, m, -C**H**), 4.61 (1H, bs, N**H**, exchanges with D_2O), 4.76 (1H, m, C**H**Ph), 5.01 (1H, td, *J* 11.0, 6.90Hz, :C**H**), 5.47 (1H, d, *J* 18.5Hz, :C**H**), 6.03 (1H, dd, *J* 11.0, 10.6Hz, :C**H**), 7.15-7.29 (6H, m, Ar**H** + :C**H**); δ_C (125.5 MHz) 23.4 (-**C**H$_3$-), 28.2 (3 x **C**H$_3$), 31.9 (-**C**H$_3$), 35.7 (-**C**H$_2$-), 45.9 (-**C**H$_2$-), 58.9 (-**C**H-), 63.8 (-**C**H-), 70.4 (-**C**(CH$_3$)$_2$), Cq), 77.1 (:**C**H), 80.1 (-**C**(CH$_3$)$_3$, Cq), 120.6 (:**C**H), 122.7 (Ar**C**), 126.9 (Ar**C**), 127.8 (Ar**C**), 129.3 (:**C**H), 131.2 (:**C**H), 141.8 (Ar**C**, Cq), 156.2 (**C**=O, Cq); *m/z* (ES$^+$) 400.2655 (100%, MH$^+$, $C_{23}H_{35}BNO_4^+$ requires 400.2659).

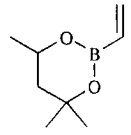
4,4,5,5-Tetrabenzyl-2-vinyl-1,3,2-dioxaborolane 271



Procedure followed as for **122** above, substituting benzopinacol (4.29 g, 11.7 mmol) for pinacol. Gave **271** as a grey powder (3.98 g, 77%) ν_{max}(KBr disc)/cm^{-1} 3097 (medium, olefinic C-H str.), 3039 (very strong, aromatic C-H str.), 2998 (strong, aliphatic C-H

str.), 1623 (strong, C=C str.), 1590, 1505 (very strong, aromatic C=C str.), 1449 (strong, aliphatic C-H def.), 1331 (very strong, B-O str.), 1247 (very strong, C-B str.), 1151 (strong, C-O str.), 1028 (medium, C-O str.); δ_H (300 MHz) 6.8-5.85 (m, 3H), 7.15 (m, 4H), 7.30 (m, 8H); δ_C (75.5 MHz) 83.4, 127.4, 127.7, 128.8, 130.5, 142.9, 144.6; *m/z* (CI^+) 403.1874(100%, MH^+, $C_{28}H_{23}BO_2$ requires 403.1869).

4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane 272[229]

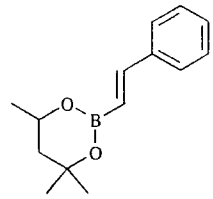


Procedure followed as for **122**, substituting *rac*-2-methyl-2,4-pentanediol (6.28 mL, 49.5 mmol) for pinacol. Gave **272** as a yellow oil that was purified by distillation (Kugelrohr, 50-55 °C at 0.3 mmHg). Recovered 5.45 g (71%) of clear oil; ν_{max}(neat)/cm^{-1} 3095 (medium, olefinic C-H str.), 3007 (strong, aliphatic C-H str.), 1622 (strong, C=C str.), 1451 (strong, aliphatic C-H def.), 1379 (strong, doublet, $-C(CH_3)_2$), 1329 (very strong, B-O str.), 1247 (very strong, C-B str.), 1153 (strong, C-O str.), 1028 (medium, C-O str.); δ_H (400 MHz) 1.23 (3H, s, CH_3), 1.26 (3H, s, $-CH_3$), 1.28 (3H, s, $-CH_3$), 1.48 (1H, m, -CH), 1.75 (1H, dd, *J* 11.2, 2.7Hz, -CH), 4.10 (1H, m, -CH), 5.81 (1H, dd, *J* 19.2, 13.5, :CH), 5.97 (1H, dd, *J* 13.5, 4.26, :CH), 6.11 (1H, dd, *J* 19.2, 4.26, :CH); δ_C (100.0 MHz) 23.3 ($-CH_3-$), 28.3 ($-CH_3-$), 31.4 ($-CH_3-$), 46.1 ($-CH_2-$), 64.9 (-CH-), 70.92 ($C(CH_3)_2$, Cq) 129.6 (B:CH), 133.96 ($:CH_2$); *m/z* (CI^+) 172.1511 (100%, $M+NH_4^+$, $C_8H_{19}BNO_2^+$ requires 172.1509)

General Procedure for Heck couplings of Aryl iodides

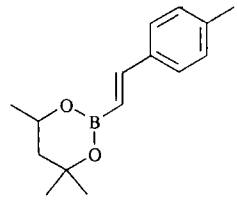
Iodobenzene (102 mg, 0.5 mmol), palladium acetate (6 mg, 5 mol %) and triphenylphosphine (16 mg, 12 mol %) were suspended in freshly distilled toluene (5 ml), and vinylboronate **272** (105 μL, 1.2 eq.) and tri-*n*-butylamine (238 μL, 2 eq.) were added. The mixture was degassed thoroughly, and heated in a sealed tube at 110 °C for 8h. After this time, the reaction was cooled and sat. NH_4Cl solution (10 mL) added. The mixture was filtered through Celite, and the filtrate extracted into EtOAc (20 mL) and washed with a) 5% HCl (2 x 10mL) b) brine (2 x 10mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The products were isolated by silica gel chromatography with 5:1 hexane / EtOAc as eluant.

4,4,6-Trimethyl-2-[(E)-2-phenylethenyl]-1,3,2-dioxaborinane 276a[230]



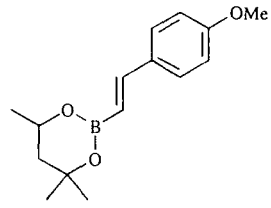
pale yellow oil; recovered 119 mg (97%) from 0.5mmol iodide; ν_{max}(film)/cm^{-1} 3030-3015 (weak, various C-H aromatic str.), 1625 (strong, C=C str.), 1511 (strong, aromatic C=C str.), 1328 (strong, B-O str.), 1250 (strong, C-B str.), 1150 (strong, C-O str.), 1030 (medium, C-O str.); δ_H (300 MHz) 1.22 (3H, s, -C**H**$_3$), 1.27 (6H, s, 2 x -C**H**$_3$), 1.41 (1H, m, -C**H**), 1.68 (1H, m, -C**H**), 4.13 (1H, m, -C**H**), 6.09 (1H, d, *J* 18.1Hz, :BC**H**), 7.11-7.18 (4H, m, Ar**H**), 7.22 (1H, dd, *J* 6.9, 1.2Hz, Ar**H**), 7.57 (1H, d, *J* 18.1Hz, :C**H**); δ_C (75.5 MHz) 22.3 (-**C**H$_3$), 24.8 (-**C**H$_3$), 31.2 (-**C**H$_3$), 46.2 (-**C**H$_2$-), 64.9 (-**C**H), 71.1 (Cq, **C**(CH$_3$)$_2$), 117.1 (b, B**C**H), 126.9 (Ar**C**), 129.1 (Ar**C**), 130.1 (Ar**C**), 135.4 (Ar**C**), 149.9 (:**C**H); *m/z* (CI$^+$) 248.1823 (70%, M+NH$_4^+$, $C_{14}H_{23}NO_2B^+$ requires 248.1822)

4,4,6-Trimethyl-2-[(*E*)-2-(4-methylphenyl)ethenyl]-1,3,2-dioxaborinane 276b



yellow solid; recovered 94 mg (77%) from 0.5mmol iodide; ν_{max}(KBr disc)/cm^{-1} 3027-3012 (weak, various C-H aromatic str.), 1623 (strong, C=C str.), 1510 (strong, aromatic C=C str.), 1330 (strong, B-O str.), 1253 (strong, C-B str.), 1152 (strong, C-O str.), 1035 (medium, C-O str.); δ_H (400MHz) 1.20 (3H, s, -C**H**$_3$), 1.24 (6H, s, 2 x -C**H**$_3$), 1.41 (1H, m, -C**H**), 1.65 (1H, m, -C**H**), 4.18 (1H, m, -C**H**), 2.24 (3H, s, -C**H**$_3$), 5.98 (1H, d, *J* 18.5Hz, :BC**H**), 7.19 (2H, d, *J* 8.1Hz, Ar**H**), 7.36 (1H, d, *J* 18.5Hz, :C**H**), 7.39 (2H, d, *J* 8.1Hz, Ar**H**); δ_C (75.5 MHz) 21.4 (Ar**C**H$_3$), 22.4 (-**C**H$_3$), 30.8 (-**C**H$_3$), 46.1 (-**C**H$_2$-), 64.8 (-**C**H-), 70.9 (Cq, **C**(CH$_3$)$_2$), 115.5 (b, :B**C**H), 126.9 (Ar**C**), 128.9 (Ar**C**), 131.5 (Cq, Ar**C**), 138.9 (Cq, Ar**C**), 151.5 (:**C**H); *m/z* (ES$^+$) 267.1536 (100%, M+Na$^+$, $C_{15}H_{21}BO_2Na^+$ requires 267.1533)

2-[(*E*)-2-(4-Methoxyphenyl)ethenyl]-4,4,6-trimethyl-1,3,2-dioxaborinane 276c



pale yellow solid; recovered 62 mg (48%) from 0.5mmol iodide; ν_{max}(KBr disc)/cm^{-1} 3020-3010 (weak, various C-H aromatic str.), 1625 (strong, C=C str.), 1508 (strong, aromatic C=C str.), 1327 (strong, B-O str.), 1251 (strong, C-B str.), 1151 (strong, C-O str.), 1030 (medium, C-O str.); δ_H (400 MHz) 1.21 (3H, s, -C**H**$_3$), 1.23 (3H, s, -C**H**$_3$), 1.25 (3H, s, -C**H**$_3$), 1.43 (1H, m, -C**H**), 1.68 (1H, dd, *J* 11.1, 2.6Hz, -C**H**), 3.68 (3H, s, -OC**H**$_3$), 4.18 (1H, m, -C**H**), 5.87 (1H, d, *J* 18.2Hz, :BC**H**), 6.98 (2H, dd, 6.8, 2.1Hz, Ar**H**), 7.33 (1H, d, 18.2Hz, :C**H**), 7.46 (2H, dd, *J* 6.8, 2.1Hz, Ar**H**); δ_C (75.5 MHz) 23.4 (-**C**H$_3$), 25.6 (-**C**H$_3$), 30.4 (-**C**H$_3$), 45.9 (-**C**H$_2$-), 55.5 (-O**C**H$_3$), 62.1 (-**C**H), 71.2 (Cq, **C**(CH$_3$)$_2$), 112.6 (Ar**C**), 115.9 (b, B**C**H), 129.5 (Ar**C**), 130.4 (Cq, Ar**C**), 149.9 (:**C**H), 160.8 (Cq, Ar**C**); *m/z* (CI$^+$) 278.1927 (100%, M+NH$_4^+$, $C_{15}H_{25}BNO_3^+$ requires 278.1928)

General Procedure for Heck coupling of bromides

p-bromotoluene (0.1 g, 5.84 mmol), palladium acetate (13 mg, 10 mol %) and triphenylphosphine (34 mg, 22 mol %) were suspended in freshly distilled toluene (5 mL). Vinylboronate **272** (122 μL, 1.2 eq) and tri-*n*-butylamine (278 μL, 2 eq) were added and the mixture was degassed thoroughly. The reaction was heated at 110°C in a sealed tube for 4 days, after which time it was cooled and quenched with sat. NH_4Cl solution (5 mL), filtered through Celite, and the filtrate extracted into EtOAc (20 mL). The organic phase was washed with a) 5% HCl (2 x 25mL) b) brine (2 x 25mL), and the combined organic phases dried over $MgSO_4$ and concentrated *in vacuo*. Products were isolated via silica gel chromatography with 6:1 hexane / EtOAc or 4:1 hexane / EtOAc as eluant.

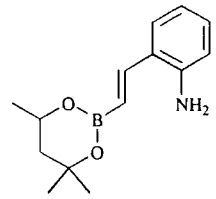
4,4,6-Trimethyl-2-[(*E*)-2-(4-methylphenyl)ethenyl]-1,3,2-dioxaborinane 276a

isolated 0.1 g (77%) from 0.1 g of *p*-bromotoluene; analytical data as quoted above.

2-[(*E*)-2-(4-Methoxyphenyl)ethenyl]-4,4,6-trimethyl-1,3,2-dioxaborinane 276b

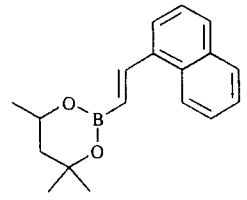
isolated 60 mg (40%) from 72 μL of *p*-bromoanisole; analytical data as quoted above.

2-[(*E*)-2-(4,4,6-Trimethyl-1,3,2-dioxaborinan-2-yl)ethenyl]phenylamine 276d



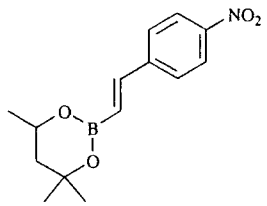
brown oil; isolated 47 mg (33%) from 0.1 g of *o*-bromoaniline ν_{max}(film)/cm^{-1} 3350 (strong, N-H str.) 3035-3016 (weak, various C-H aromatic str.), 1620 (strong, C=C str.), 1510 (strong, aromatic C=C str.), 1325 (strong, B-O str.), 1249 (strong, C-B str.), 1150 (strong, C-O str.), 1032 (medium, C-O str.); δ_H (300 MHz) 1.22 (3H, s, -C**H**$_3$), 1.26 (3H, s, -C**H**$_3$), 1.32 (3H, s, -C**H**$_3$), 1.40 (1H, m, -C**H**), 1.59 (1H, dd, *J* 11.1, 3.0Hz, -C**H**), 3.58 (2H, bs, -N**H**$_2$), 4.17 (1H, m, -C**H**), 6.22 (1H, d, *J* 18.2Hz, BC**H**), 6.77 (1H, dd, *J* 7.9, 1.6Hz, Ar**H**), 7.26 (1H, t, *J* 7.9Hz, Ar**H**), 7.35 (1H, t, *J* 7.9Hz, Ar**H**), 7.47 (1H, d, *J* 18.2Hz, :C**H**); δ_C (75.5 MHz) 22.4 (-**C**H$_3$), 24.5 (-**C**H$_3$), 31.2 (=**C**H$_3$), 46.1 (-**C**H$_2$-), 62.3 (-**C**H), 70.8 (Cq, -**C**(CH$_3$)$_2$), 115.7 (b, B**C**H), 119.8 (Ar**C**), 121.9 (Ar**C**), 123.7 (Cq, Ar**C**), 126.8 (Ar**C**), 130.1 (Ar**C**), 148.2 (Cq, Ar**C**), 148.6 (:**C**H); *m/z* (CI$^+$) 263.1931 (80%, M+NH$_4^+$, $C_{14}H_{24}BN_2O_2^+$ requires 263.1927)

4,4,6-Trimethyl-2-[(*E*)-2-(1-naphthyl)ethenyl]-1,3,2-dioxaborinane 276e



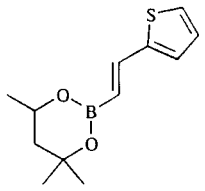
colourless oil; isolated 67 mg (50%) from 0.1g 1-bromonaphthalene; ν_{max}(film)/cm^{-1} 1610 (strong, C=C str.), 1507 (strong, aromatic C=C str.), 1321 (strong, B-O str.), 1251 (strong, C-B str.), 1150 (strong, C-O str.), 1030 (medium, C-O str.); δ_H (400 MHz) 1.23 (3H, s, -C**H**$_3$), 1.27 (3H, s, -C**H**$_3$), 1.30 (3H, s, -C**H**$_3$), 1.43 (1H, m, -C**H**), 1.62 (1H, m, -C**H**), 4.1 (1H, m, -C**H**), 6.21 (1H, d, *J* 18.3Hz, BC**H**), 7.41-7.55 (3H, m, Ar**H**), 7.79-7.91 (3H, m, Ar**H**), 8.25 (1H, d, *J* 18.3Hz, :C**H**), 8.29 (1H, d, *J* 8.0Hz, Ar**H**); δ_C (75.5 MHz) 24.4 (-**C**H$_3$), 25.6 (-**C**H$_3$), 31.5 (-**C**H$_3$), 46.9 (-**C**H$_2$), 63.3 (-**C**H), 71.5 (Cq, **C**(CH$_3$)$_2$), 118.8 (b, B**C**H), 122.9 (Ar**C**), 123.5 (Ar**C**), 126.9 (Ar**C**), 127.0 (Ar**C**), 127.1 (Ar**C**), 127.3 (Ar**C**), 128.1 (Ar**C**), 128.8 (Ar**C**), 133.3 (Cq, Ar**C**), 136.9 (Cq, Ar**C**), 151.4 (:**C**H); *m/z* (CI$^+$) 298.1977 (100%, M+NH$_4^+$, $C_{18}H_{25}BNO_2^+$ requires 298.1979)

4,4,6-Trimethyl-2-[(*E*)-2-(4-nitrophenyl)ethenyl]-1,3,2-dioxaborinane 276f



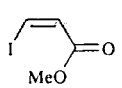
pale yellow oil; isolated 267 mg (51%) from 0.1g *p*-bromonitrobenzene; ν_{max}(film)/cm^{-1} 3040-3022 (weak, various C-H aromatic str.), 1628 (strong, C=C str.), 1512 (strong, aromatic C=C str.), 1320 (strong, B-O str.), 1254 (strong, C-B str.), 1153 (strong, C-O str.), 1030 (medium, C-O str.); δ_H (300 MHz) 1.21 (3H, s, -C**H**$_3$), 1.26 (3H, s, -C**H**$_3$), 1.31 (3H, s, -C**H**$_3$), 1.42 (1H, m, -C**H**), 1.66 (1H, m, -C**H**), 4.15 (1H, m, -C**H**), 6.35 (1H, d, *J* 18.5Hz, BC**H**), 7.47 (1H, d, *J* 18.5Hz, :C**H**), 7.67 (2H, d, *J* 8.5Hz, Ar**H**), 8.22 (2H, d, *J* 8.5Hz, Ar**H**); δ_C (75.5 MHz) 23.4 (-**C**H$_3$), 25.5 (-**C**H$_3$), 30.9 (-**C**H$_3$), 46.1 (-**C**H$_2$-), 62.8 (-**C**H), 71.1 (Cq, **C**(CH$_3$)$_2$), 116.3 (b, B**C**H), 125.4 (Ar**C**), 128.1 (Ar**C**), 140.4 (Cq, Ar**C**), 148.9 (Cq, Ar**C**), 150.1 (:**C**H); *m/z* (CI$^+$) 293.1671 (75%, M+NH$_4^+$, $C_{14}H_{22}BN_2O_4^+$ requires 293.1673)

4,4,6-Trimethyl-2-[(*E*)-2-(2-thienyl)ethenyl]-1,3,2-dioxaborinane 276g



light brown oil; isolated 106 mg (77%) from 56μL 2-bromothiophene; ν_{max}(film)/cm^{-1} 1618 (strong, C=C str.), 1510 (strong, aromatic C=C str.), 1328 (strong, B-O str.), 1250 (strong, C-B str.), 1150 (strong, C-O str.), 1031 (medium, C-O str.); δ_H (400 MHz) 1.22 (3H, s, -C**H**$_3$), 1.25 (3H, s, -C**H**$_3$), 1.29 (3H, s, -C**H**$_3$), 1.42 (1H, m, -C**H**), 1.66 (1H, m, -C**H**), 4.19 (1H, m, -C**H**), 5.80 (1H, d, *J* 18.1Hz, BC**H**), 6.89 (1H, dd, *J* 5.1, 3.4Hz, Ar**H**), 7.09 (1H, d, *J* 3.4Hz, Ar**H**), 7.34 (1H, d, *J* 5.1Hz, Ar**H**), 7.59 (1H, d, *J* 18.1Hz, :C**H**); δ_C (125.5MHz) 23.4 (-**C**H$_3$), 25.7 (-**C**H$_3$), 30.4 (-**C**H$_3$), 45.1 (-**C**H$_2$-), 62.7 (-**C**H), 70.5 (Cq, **C**(CH$_3$)$_2$), 113.9 (b, B**C**H), 127.1 (Ar**C**), 128.9 (Ar**C**), 130.5 (Ar**C**), 142.2 (Cq, Ar**C**), 147.8 (:**C**H); *m/z* (CI$^+$) 237.1121 (100%, MH$^+$, $C_{12}H_{18}BO_2S^+$ requires 237.1121).

Methyl (Z)-3-iodo-2-propenoate 214[190]

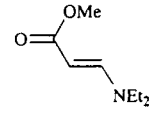


Methyl propiolate (2.50 g, 30 mmol), sodium iodide (7.13 g, 48 mmol) and glacial acetic acid (10.9 mL, 102 mmol) were stirred at 115 °C under argon for 1 hour. The hot reaction was poured into 100 mL of water, and extracted with diethyl ether (50 mL). The phases were separated and the aqueous phase extracted with diethyl ether (2 x 25mL). The combined organic phases were washed with a) saturated Na_2CO_3, b) saturated $Na_2S_2O_3$ and brine, before drying ($MgSO_4$). Concentration gave **214** as a colourless oil (4.77 g, 75%) ν_{max} (neat)/cm^{-1} 2950 (medium, alpihatic C-H str.), 1730 (strong, C=O str.), 1600 (strong, C=C str., conj.), 1440 (strong, aliphatic C-H def.), 1340 (strong, $-CH_3$ sym. def.), 1200 (2 bands, strong, C-O str.); δ_H (300 MHz) 3.8 (3H, s, $-OCH_3$), 6.91 (1H, d, *J* 9Hz, :CHI), 7.55 (1H, d, *J* 9Hz, MeO_2C-CH:); δ_C (75.5 MHz) 52.0 ($-OCH_3$), 95.5 (:CHI), 129.9 (MeO_2C-CH:), 165.2 (MeO_2C-); *m/z* (CI^+) 212.0038 (100%, MH^+, $C_4H_6IO_2^+$ requires 212.0036).

Representative procedure for the formation of amino acrylates 290

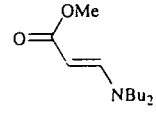
Iodoacrylate (0.7 g, 0.0033 mol) and amine (2 eq.) were refluxed in dry toluene or acetonitrile (3 mL) until TLC indicated consumption of iodoacrylate. After this time, the cooled reaction was filtered to remove the salts **291**, and the filtrate washed with 5% HCl and distilled water. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (typically 4:1 hexane / ethyl acetate) gave the pure amino acrylates;

Methyl (*E*)-3-(diethylamino)-2-propenoate 290a[191]



brown oil; ν_{max}(film)/cm^{-1} 1689 (strong, C=O str.), 1607 (strong, C=C str., conj.); δ_H (300 MHz) 1.15 (6H, t, *J* 7, 2xCH_3); 3.15 (4H, q, *J* 7, 2xCH_2); 3.63 (3H, s, $-OCH_3$); 4.57 (1H, d, *J* 13.3, :CH); 7.45 (1H, d, *J* 13.3, :CH) δ_C (75.5 MHz) 15.0 ($-CH_3$); 42.7 ($-CH_2$-); 50.7 ($-OCH_3$); 83.3 (:CH); 151.4 (:CH); 170.7 (Cq, C=O) *m/z* (ES^+) 158.1178 (100%, MH^+, $C_8H_{16}NO_2^+$ requires 158.1181)

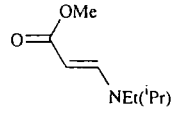
Methyl (*E*)-3-(dibutylamino)-2-propenoate 290b



light yellow oil; ν_{max}(film)/cm^{-1} 1689 (strong, C=O str.), 1611 (C=C str., conj.); δ_H (300 MHz) 0.90 (t, 6H, *J* 7.5Hz, 2xCH_3); 1.27 (4H, m, 2xCH_2); 1.50 (4H, m, 2xCH_2); 3.10 (4H, bm, 2xCH_2); 3.62 (3H, s, $-OCH_3$); 4.50 (1H, d, *J* 13.2, :CH); 7.41 (1H, d, *J* 13.2, :CH) δ_C (75.5 MHz) 14.3 ($-CH_3$-); 20.3 ($-CH_2$-); 29.3 ($-CH_2$-);50.6 ($-OCH_3$-); 55.5 (-

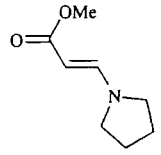
CH_2-); 83.6 (:CH); 152.1 (:CH); 170.5 (Cq, C=O) *m/z* (ES^+) 214.1808 (100%, MH^+, $C_{12}H_{24}NO_2^+$ requires 214.1807).

Methyl (*E*)-3-[ethyl(isopropyl)amino]-2-propenoate 290c[195]



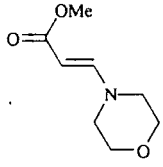
yellow oil, ν_{max}(film)/cm^{-1} 1685 (strong, C=O str.), 1600 (C=C str., conj.); δ_H (300 MHz) 1.10-1.25 (9H, m,); 3.12 (2H, q, *J* 7.5, -CH_2); 3.5 (1H, m, *J* 7.5, -CH); 3.65 (3H, s, -OCH_3); 4.55 (1H, d, *J* 13.7, :CH); 7.50 (1H, d, *J* 13.7, :CH); δ_C (75.5 MHz) 11.7 (-CH_3); 21.3 (-$CH(CH_3)_2$); 40.0 (-NCH_2CH_3); 47.0 (-$CH(CH_3)_2$); 49.3 (-OCH_3); 82.1 (:CH); 148.4 (:CH); 169.4 (Cq, C=O) *m/z* (ES^+) 172.1335 (100%, MH^+, $C_9H_{18}NO_2^+$ requires 172.1337).

Methyl (*E*)-3-(1-pyrrolidinyl)-2-propenoate 290d[191]



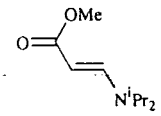
yellow crystalline solid; ν_{max}(film)/cm^{-1} 1689 (C=O. str.), 1615 (C=C str., conj.); δ_H (300 MHz) 1.90 (bm, 4H, 2xCH_2); 3.1 (bm, 4H, 2xCH_2); 3.60 (3H, s, -OCH_3); 4.45 (1H, d, *J* 13.1, :CH); 7.60 (1H, d, *J* 13.1, :CH); δ_C (75.5 MHz) 24.2 (-CH_2-); 49.3 (-CH_2-); 83.2 (:CH); 147.7 (:CH); 168.9 (Cq, C=O); *m/z* (ES^+) 156.1025 (100%, MH^+, $C_8H_{14}NO_2^+$ requires 156.1024).

Methyl (*E*)-3-(4-morpholinyl)-2-propenoate 290e[191]



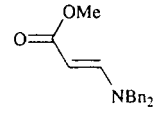
light yellow crystalline solid; ν_{max}(film)/cm^{-1} 1689 (C=O str.), 1607 (C=C str., conj.); δ_H (300 MHz) 3.17 (4H, t, *J* 7, 2xCH_2); 3.65 (7H, m, -OCH_3 and 2xCH_2); 4.67 (1H, d, *J* 13.4, :CH); 7.33 (1H, d, *J* 13.4, :CH) δ_C (75.5 MHz) 47.6 (-CH_2-); 50.3 (-OCH_3); 65.1 (-CH_2-); 84.9 (:CH); 150.8 (:CH); 168.8 (Cq, C=O); *m/z* (ES^+) 172.0969 (100%, MH^+, $C_8H_{14}NO_3^+$ requires 172.0973).

Methyl (*E*)-3-(diisopropylamino)-2-propenoate 290f[191]



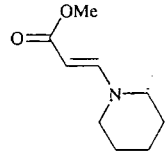
light yellow oil; ν_{max}(film)/cm^{-1} 1689 (C=O str.), 1600 (C=C str., conj.); δ_H (300 MHz) 1.15 (12H, s, 2x-(CH_3)$_2$); 3.60 (5H, bs, -OCH_3 and 2xCH); 4.65 (1H, d, *J* 13.5, :CH); 7.55 (1H, d, *J* 13.5, :CH) δ_C (75.5 MHz) 20.5 (b, -CH_3); 47.0 (-CH-); 49.3 (-OCH_3-); 82.1 (:CH); 146.2 (:CH); 169.4 (Cq, C=O) *m/z* (ES$^+$) 186.1492 (100%, MH$^+$, $C_{10}H_{20}NO_2^+$ requires 186.1494).

Methyl (*E*)-3-(dibenzylamino)-2-propenoate 290g[191]



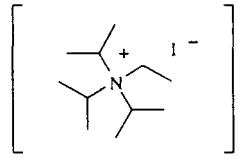
yellow oil; ν_{max}(film)/cm^{-1} 1693 (C=O str.,), 1607 (C=C str., conj.); δ_H (300 MHz) 3.68 (3H, s, -OCH_3); 4.30 (4H, bs, 2xCH_2); 4.83 (1H, d, *J* 13.1, :CH); 7.41-7.13 (10H, m, ArH); 7.83 (1H, d, *J* 13.1, :CH) δ_C (75.5 MHz) 37.6 (-CH_2-); 51.7 (-OCH_3); 85.9 (:CH); 126.9 (ArC); 128.8 (ArC); 130.1 (ArC); 138.2 (ArCq); 153.2 (:CH); 170.6 (Cq, C=O) *m/z* (ES$^+$) 282.1493 (100%, MH$^+$, $C_{18}H_{16}NO_2^+$ requires 282.1494)

Methyl (*E*)-3-(1-piperidinyl)-2-propenoate 290h[191]



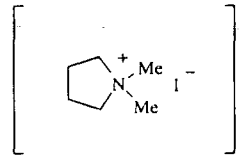
yellow powder; ν_{max}(KBr disc)/cm^{-1} 1705 (C=O str.), 1610 (C=C str., conj.); δ_H (300 MHz) 1.60 (6H, bs, 3xCH_2), 3.19 (4H, bs, 2xCH_2), 3.65 (3H, s, -OCH_3), 4.61 (1H, d, *J* 13.1, :CH), 7.40 (1H, d, *J* 13.1, :CH) δ_C (75.5 MHz) 24.5 (-CH_2), 25.8 (-CH_2), 50.8 (-OCH_3), 52.0 (-CH_2), 83.6 (=CH), 152.5 (=CH), 170.9 (Cq, C=O); *m/z* (ES$^+$) 170.1180 (100%, MH$^+$, $C_9H_{16}NO_2^+$ requires 170.1181)

***N*-Ethyl-*N*,*N*-diisopropyl-2-propanaminium iodide 291c**[195]



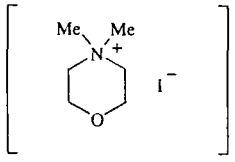
white crystalline solid (70%); δ_H (D_2O, 300 MHz) 1.28 (t, 3H, *J* 6.9Hz, CH_3CH_2-), 1.57 (18H, m, 3x(-CH_3)$_2$), 3.06 (2H, bm, CH_3CH_2-), 4.52 (3H, bm, 3xCH-); δ_C (D_2O, 75.5 MHz) 10.1 (-CH_3CH_2-), 18.7 (-CH_3), 49.5 (-CH_2-), 57.3 (-CH-); *m/z* (ES$^+$) 172.2065(100%, (M-I)$^+$, $C_{11}H_{26}N^+$ requires 172.2059)

1,1-Dimethylpyrrolidinium iodide 291d[231]



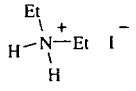
off-white crystalline solid (74%); δ_H (D_2O, 300 MHz) 2.24 (4H, m, 2x-CH_2), 3.38 (6H, s, 2xCH_3), 3.69 (4H, m, 2xCH_2); δ_C (D_2O, 75.5 MHz) 21.9 (-CH_2-), 52.6 (-CH_3), 68.7 (-CH_2-); *m/z* (ES^+) 116.1077 (100%, $(M-I)^+$, $C_6H_{14}NO^+$ requires 116.1075)

4,4-Dimethylmorpholin-4-ium iodide 291e[232]



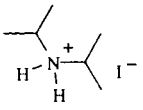
off-white crystalline solid (86%); δ_H (D_2O, 300 MHz) 3.16 (6H, s, 2 x CH_3), 3.41 (4H, t, *J* 6.28Hz, 2 x CH_2-), 3.95 (4H, bm, 2 x -CH_2-); δ_C (D_2O, 75.5 MHz) 54.7 (-CH_3), 64.8 (-CH_2-), 64.9 (-CH_2-); *m/z* (ES^+) 116.1077 (100%, $(M-I)^+$, $C_6H_{14}NO^+$ requires 116.1075).

***N*-Ethyl-1-ethanaminium iodide 291f**[195]



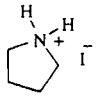
white crystalline solid (83%); δ_H (D_2O, 300 MHz) 1.18 (6H, t, *J* 8.15, 2 x -CH_3), 2.98 (4H, q, *J* 7.16Hz, 2x -CH_2); δ_C (D_2O, 75.5 MHz) 12.1 (-CH_3), 44.5 (-CH_2-); *m/z* (ES^+) 74.0966 (100%, $(M-I)^+$, $C_4H_{12}N^+$ requires 74.0969).

***N*-Isopropyl-2-propanaminium iodide 291g**[195]



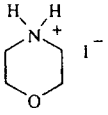
white crystalline solid (77%); δ_H (D_2O, 300 MHz) 1.17 (6H, s, 2 x -CH_3), 1.19 (6H, s, 2 x -CH_3), 3.40 (2H, m, 2x -CH-); δ_C (D_2O, 75.5 MHz) 19.8 (-CH_3), 48.8 (-CH-); *m/z* (ES^+) 102.1281 (100%, $(M-I)^+$, $C_6H_{16}N^+$ requires 102.1283).

1,1-Dimethylpyrrolidinium iodide 291h[195]



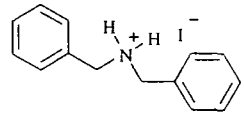
off-white solid (72%); δ_H (D_2O, 300 MHz) 1.89 (4H, m, -CH_2-), 3.18 (4H, m, -CH_2-); δ_C (D_2O, 75.5 MHz) 24.1 (-CH_2-), 46.1 (-CH_2-); *m/z* (ES^+) 72.0813 (100%, $(M-I)^+$, $C_4H_{10}N^+$ requires 72.0813).

Morpholin-4-ium iodide 291i[195]



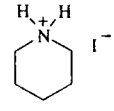
beige solid (72%); δ_H (D_2O, 300 MHz) 2.99 (4H, bs, -CH_2-), 3.74 (4H, bs, -CH_2-); δ_C (D_2O, 75.5 MHz) 44.2 (-CH_2-), 65.6 (-CH_2-); *m/z* (ES^+) 88.0760 (100%, $(M-I)^+$, $C_4H_{10}NO^+$ requires 88.0762).

<u>*N*-Benzyl(phenyl)methanaminium iodide 291j</u>[195]



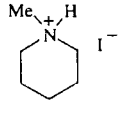
yellow solid; δ_H (D_2O, 300 MHz) 4.20 (4H, bs, 2 x -CH_2-), 7.43-7.49 (10H, m, Ar**H**); δ_C (D_2O, 75.5 MHz) 51.4 (-CH_2-), 128.6 (Ar**C**), 129.5 (Ar**C**), 129.9 (Ar**C**), 130.8 (Ar**C**, Cq); *m/z* (ES^+) 198.1283 (100%, $(M-I)^+$, $C_{14}H_{16}N^+$ requires 198.1282)

<u>Piperidinium iodide 291k</u>[195]



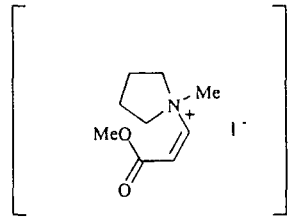
off-white solid (91%); δ_H (D_2O, 300 MHz) 1.56 (2H, m, -CH_2-), 1.66 (4H, m, -CH_2-), 3.05 (4H, t, *J* 6.75Hz, -CH_2-); δ_C (D_2O, 75.5 MHz) 21.9 (-CH_2-), 22.6 (-CH_2-), 44.9 (-CH_2-); *m/z* (ES^+) 86.0971 (100%, $(M-I)^+$, $C_5H_{12}N^+$ requires 86.0969).

<u>1-Methylpiperidinium iodide 291l</u>[195]



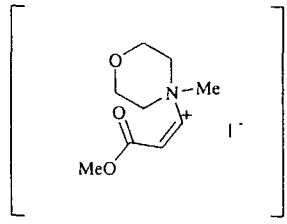
off-white solid (88%) δ_H (D_2O, 300 MHz) 1.55 (2H, m, -CH_2-), 1.78 (4H, bm, -CH_2-), 3.00 (3H, bs, -CH_3), 3.24 (4H, t, *J* 6.38Hz, -CH_2-); δ_C (D_2O, 75.5 MHz) 21.9 (-CH_2-), 23.9 (-CH_2-), 44.7 (-CH_3), 57.4 (-CH_2-); *m/z* (ES^+) 100.1124 (100%, $(M-I)^+$, $C_6H_{14}N^+$ requires 100.1126).

<u>1-[(Z)-3-Methoxy-3-oxo-1-propenyl]-1-methylpyrrolidinium iodide 293d</u>[195]



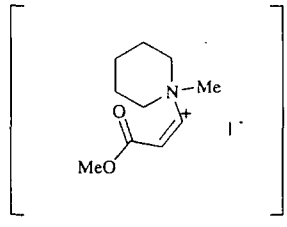
white solid; δ_H (400MHz, D_2O) 2.18 (4H, bm, -CH_2-), 3.44 (3H, s, -N**C**H_3), 3.78 (3H, s, -O**C**H_3), 3.89 (4H, bm, -CH_2-), 6.19 (1H, d, *J* 9.70 Hz, :C**H**), 6.65 (1H, d, *J* 9.70 Hz, :C**H**); δ_C (75.5MHz, D_2O) 21.8 (-CH_2-), 50.9 (-N**C**H_3), 53.7 (-O**C**H_3), 68.9 (-CH_2-), 120.3 (:CH), 147.4 (:CH), 164.6 (Cq, C=O); *m/z* (ES^+) 170.1178 (100%, $(M-I)^+$, $C_9H_{16}NO_2^+$ requires 170.1181)

4-[(Z)-3-Methoxy-3-oxo-1-propenyl]-4-methylmorpholin-4-ium iodide 293e[195]



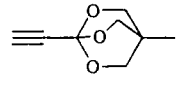
white solid; δ_H (400 MHz, D_2O) 3.53 (3H, s, NCH_3), 3.73 (3H, s, $-OCH_3$), 3.89-4.12 (8H, bm, 4x-CH_2), 6.32 (1H, d, *J* 10.4Hz, :CH), 6.58 (1H, d, *J* 10.4Hz, :CH); δ_C (75.5 MHz, D_2O) 53.7 ($-NCH_3$), 54.2 ($-OCH_3$), 62.1 ($-CH_2-$), 64.1 ($-CH_2-$) 122.0 (:CH), 140.5 (:CH), 164.3 (Cq, C=O); *m/z* (ES^+) 186.1129 (100%, $(M-I)^+$, $C_9H_{16}NO_3^+$ requires 186.1130).

1-[(Z)-3-Methoxy-3-oxo-1-propenyl]-1-methylpiperidinium iodide 293l[195]



white solid; δ_H (400 MHz, D_2O) 1.48 (2H, bm, $-CH_2-$) 1.66-1.82 (4H, bm, $-CH_2-$), 3.40 (3H, s, $-NCH_3$), 3.37-3.46 (4H, bm, $-CH_2-$), 3.74 (3H, s, $-OCH_3$), 6.24 (1H, d, *J* 10.4Hz, :CH), 6.43 (1H, d, *J* 10.4Hz, :CH); δ_C (75.5 MHz, D_2O) 20.2 ($-CH_2-$), 21.3 ($-CH_2-$), 53.8 ($-NCH_3$), 54.1 ($-OCH_3$), 65.7 ($-CH_2-$), 121.0 (:CH), 140.6 (:CH), 164.8 (Cq, C=O); *m/z* (ES^+) 184.1337 (100%, $(M-I)^+$, $C_{10}H_{18}NO_2^+$ requires 184.1337)

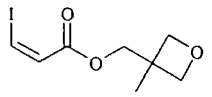
1-Ethynyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane 301[198]



To a solution of oxetane ester **305** (2.00 g, 12.9 mmol) in anhydrous DCM (10mL) stirred at -15 °C under argon was added $BF_3.Et_2O$ (0.37 mL, 2.9 mmol). The mixture was stirred at -15 °C for 18h, then quenched by the addition of Et_3N (1.6 mL). After diluting with Et_2O and filtering, the filtrate was concentrated and filtered through silica gel pretreated with Et_3N to afford **301** as a white waxy solid; 0.76 g (38%); ν_{max}(KBr disc)/cm^{-1} 3290 (strong, C-H str. alkyne), 2115 (weak, C≡C str.); δ_H (300MHz) 0.82 (3H, s, $-CH_3$), 2.56 (1H, s, -C≡CH), 3.98 (6H, s, 3xCH_2); δ_C (75.5MHz) 14.7 ($-CH_3$),

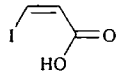
30.6 (Cq, $C(CH_2O)_3$, 70.9 (≡CH), 73.4 (-CH_2-), 77.9 (Cq, C≡CH), 101.7 (Cq, $C(OCH_2)_3$); *m/z* (ES^+) 155.0709 (100%, MH^+, $C_8H_{11}O_3^+$ requires 155.0708)

(3-Methyl-3-oxetanyl)methyl (Z)-3-iodo-2-propenoate 302[233]



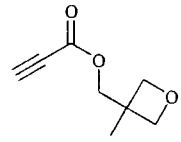
To a solution of 3-(hydoxymethyl)-3-methyloxetane **303** (2.50 mL, 25.0 mmol), DCC (7.30 g, 35.0 mmol) and DMAP (200 mg) in anhydrous DCM (80 mL) stirred at 0 °C under argon was added **304** (5.00 g, 25.0 mmol) over 2.5h. The mixture was diluted with DCM (100 mL), filtered to remove the urea by-product, and the filtrate washed with a) 1% NH_4Cl (30 mL) b) $NaHCO_3$ (30 mL) and finally H_2O (30 mL). The organic phase was dried over $MgSO_4$ and concentrated to give a dark brown oil (7.82 g) that was double distilled (Kugelrohr, 110 °C, 0.5 mmHg) to give pure **302** as a yellow oil (5.85 g, 82%) ν_{max}(film)/cm^{-1} 1730 (strong, C=O str.), 1620 (strong, C=C str.); δ_H (400 MHz) 1.37 (3H, s, -CH_3), 4.29 (2H, s, -CH_2), 4.4 (2H, d, *J* 6.1Hz, -CH_2), 4.54 (2H, d, *J* 6.1Hz, -CH_2), 6.91 (1H, d, *J* 9.9Hz, :CH), 7.49 (1H, d, *J* 9.9Hz, :CHI); δ_C (100 MHz) 21.2 (-CH_3), 39.4 (Cq, -$C(CH_3)$), 69.4 (-CH_2O), 79.9 (-CH_2-), 96.0 (:CHI), 130.0 (:CH), 164.9 (Cq, C=O); *m/z* (CI^+) 300.0097 (100%, $M+NH_4^+$, $C_8H_{15}INO_3^+$ requires 300.0097).

(Z)-3-Iodo-2-propenoic acid 304[199]



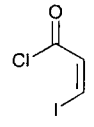
To a solution of 55% aqueous HI (20 mL) and H_2O (30 mL) was added propiolic acid (7.00 g, 100.0 mmol). The mixture was heated at 50 °C for 17h, then cooled and diluted with Et_2O. The layers were separated, and the aqueous layer extracted with Et_2O. The combined organic phases were washed with H_2O and dried over $MgSO_4$. After removing the solvent *in vacuo*, the residue was washed with cold hexane affording pure **304** as a pale yellow solid (17.4 g, 88%); m.p. 66-68°C, lit. value 66-67°C;[199] ν_{max}(KBr disc)/cm^{-1} 3120-2560 (several strong bands, O-H str. H-bonding), 1727 (C=O str.), 1612 (C=C str.); δ_H (300 MHz) 6.98 (1H, d, *J* 9.8Hz, :CH), 7.71 (1H, d, *J* 9.8Hz, :CHI), 11.9 (1H, s, -OH); δ_C (75.5 MHz) 99.0 (:CHI), 129.9 (:CH), 170.6 (Cq, C=O); *m/z* (CI^+) 215.9520 (100%, $M+NH4^+$, $C_3H_7INO_2^+$ requires 215.9522)

(3-Methyl-3-oxetanyl) methyl propiolate 305[198]



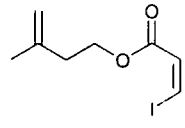
To a solution of 3-(hydoxymethyl)-3-methyloxetane (20.0 g, 196.0 mmol), DCC (57.0 g, 276.0 mmol) and DMAP (1.2 g) in anhydrous DCM (80 mL) stirred at 0 °C under argon was added propiolic acid (13.8 g, 196.0 mmol) over 2.5h. The mixture was diluted with DCM (100 mL), filtered to remove the urea by-product, and the filtrate washed with a) 1% NH_4Cl (250 mL) b) $NaHCO_3$ (250 mL) and finally H_2O (250 mL). The organic phase was dried over $MgSO_4$ and concentrated to give a dark red oil (26.3 g) that was distilled (75 °C, 0.5 mmHg) to give pure **305** as a colourless oil (15.9 g, 53%) ν_{max}(film)/cm^{-1} 3297 (strong, C-H alkyne str.), 2120 (weak, C≡C str.), 1715 (C=O str.); δ_H (300 MHz) 1.37 (3H, s, -C**H**$_3$), 2.96 (1H, s, ≡C**H**), 4.29 (2H, s, -C**H**$_2$-), 4.43 (2H, d, *J* 6Hz, -C**H**$_2$), 4.52 (2H, d, *J* 6Hz, -C**H**$_2$); δ_C (75.5 MHz) 21.1 (-**C**H$_3$), 39.4 (Cq, -**C**(CH$_3$)), 68.4 (-**C**H$_2$), 74.7 (≡**C**H), 75.9 (Cq, ≡**C**-), 79.7 (-**C**H$_2$-), 153.1 (Cq, **C**=O); *m/z* (ES$^+$) 155.0707 (100%, MH$^+$, $C_8H_{11}O_3^+$ requires 155.0708)

(Z)-3-Iodo-2-propenoyl chloride 306[234]



Oxalyl chloride (6.00 mL, 0.067 mol) was added dropwise with stirring to a solution of **304** (5.00 g, 0.025 mol) in anhydrous DCM (60mL). After stirring at room temperature for 12h, the solvent was removed *in vacuo*, giving a noxious and lachrymatory light brown liquid (5.13 g, 94%) that was used without further purification. An analytically pure sample was obtained by distillation (75 °C, 0.5 mmHg); ν_{max}(film)/cm^{-1} 1734 (strong, C=O str.), 1605 (C=C str.); δ_H (300 MHz) 7.13 (1H, d, *J* 8.9Hz, :C**H**), 8.45 (1H, d, *J* 8.9Hz, :C**H**I); δ_C (75.5 MHz) 108.8 (:**C**HI), 140.7 (:**C**H). 164.3 (Cq, **C**=O); *m/z* (CI$^+$).233.9180 (100%, M+NH$_4^+$, $C_3H_6NOICl^+$ requires 233.9183)

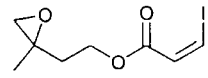
3-Methyl-3-butenyl (Z)-3-iodo-2-propenoate 308



To a solution of **304** (5.00 g, 0.023 mol) in anhydrous DCM (20 mL) cooled to 0 °C was added 3-methyl-3-buten-1-ol **307** (2.33 mL, 0.023 mol) followed by Et_3N (3.11 mL, 0.023 mol) dropwise. The reaction was stirred at RT for 1h, after which time ^{1}H NMR indicated the reaction was complete. The reaction was diluted with DCM, washed with

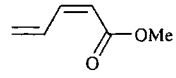
5% HCl (50mL) and brine, before being dried over $MgSO_4$. Removal of solvents *in vacuo* gave a brown oil that was doubly-distilled (Kugelrohr, 75-85 °C, 0.5 mmHg) to give the title compound as a yellow liquid 2.56 g (42%); ν_{max}(film)/cm^{-1} 1725 (strong, C=O str.), 1630 (strong, C=C str.), 1611 (medium, C=C str.); δ_H (300 MHz) 1.76 (3H, s, -C**H**$_3$), 2.39 (2H, t, *J* 6.9Hz, -C**H**$_2$-), 4.31 (2H, t, *J* 6.9Hz, -C**H**$_2$O-), 4.78 (1H, s, :C**H**), 4.84 (1H, s, :C**H**), 6.91 (1H, d, *J* 8.9Hz, :C**H**), 7.46 (1H, d, *J* 8.9Hz, :C**H**I); δ_C (75.5 MHz) 22.9 (-**C**H$_3$), 37.0 (-**C**H$_2$-), 63.4 (-**C**H$_2$O-), 95.4 (:**C**HI), 113.4 (:**C**H$_2$), 141.8 (Cq, **C**:CH$_2$), 164.9 (Cq, **C**=O); *m/z* (CI$^+$) 284.0146 (100%, M+NH4$^+$, $C_8H_{15}INO_2^+$ requires 284.0148)

2-(2-Methyl-2-oxiranyl)ethyl (Z)-3-iodo-2-propenoate 309



A solution of iodo-ester **308** (250 mg, 0.94 mmol) in dry DCM (5mL) was treated portionwise with *m*-CPBA (284 mg, 1.5eq of a 57% w/w peroxide mixture) at 0 °C. The mixture was at RT for 5h, then cooled to 0 °C and filtered. The filtrate was washed with 5% KOH solution, and brine. The organic phase was dried and concentrated *in vacuo* to give a crude oil that was purified by column chromatography (SiO_2, 1:1 Et_2O / hexane) to yield pure epoxyester **309** as a light yellow oil: 143 mg (53%), ν_{max}(film)/cm^{-1} 1728 (strong, C=O str.), 1627 (strong, C=C str.); δ_H (400 MHz) 1.36 (3H, s, -C**H**$_3$), 2.04 (2H, m, -C**H**$_2$-), 2.60 (1H, d, *J* 4.7Hz, -C**H**), 2.69 (1H, d, *J* 4.7Hz, -C**H**), 4.31 (2H, t, *J* 6.6Hz, -C**H**$_2$O-), 6.91 (1H, d, *J* 8.8Hz, :C**H**), 7.47 (1H, d, *J* 8.8Hz, :C**H**I); δ_C (75.5 MHz) 20.9 (-**C**H$_3$), 38.8 (-**C**H$_2$-), 54.8 (Cq, **C**(CH$_3$)), 55.9 (-**C**H$_2$-), 63.1 (-**C**H$_2$O-), 95.8 (:**C**HI), 131.1 (:**C**H), 164.7 (Cq, **C**=O); *m/z* (CI$^+$) 300.0093 (100%, M+NH$_4^+$, $C_8H_{15}INO_3^+$ requires 300.0097)

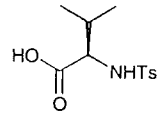
Methyl (2*Z*)-2,4-pentadienoate 311[235]



Iodoacrylate **214** (0.33 mL, 2.95 mmol) and palladium acetate (66 mg, 10 mol %) were dissolved in dry MeCN (5mL). Silver carbonate (1.2 g, 1.5 eq.) and vinylboronate **122** (1.4 mL of a 60% solution in THF, 2 eq.) were added and the mixture degassed thoroughly, before being allowed to stir under Ar at ambient temperature overnight. The reaction was diluted with MeCN (10 mL), filtered through a cotton wool plug, washed with 5% HCl (2 x 25 mL) and brine (2 x 20 mL), and the organic layer was dried over $MgSO_4$. Concentration gave a dark yellow oil that was purified by chromatography following adsorption onto silica gel (6:1 hexane / ethyl acetate as

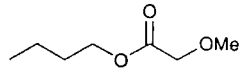
eluant). Gave the Suzuki product **311** exclusively as a pale yellow oil; 224 mg (68%); ν_{max}(film)/cm^{-1} 1710 (strong, C=O str.), 1625 (medium, C=C str.); δ_H (400 MHz) 3.41 (3H, s, -OMe), 5.47 (1H, d, *J* 11.2Hz, :C**H**), 5.55 (1H, dd, *J* 10.5, 1.8Hz, :C**H**), 5.66 (1H, dd, *J* 16.8, 1.8Hz, :C**H**), 6.63 (1H, dd, *J* 16.8, 10.5Hz, :C**H**); 6.89 (1H, d, *J* 11.2Hz, :C**H**); δ_C (75.5 MHz) 50.3 (-OMe), 116.50 (:CH_2), 117.9 (:CH), 132.6 (:CH). 137.6 (:CH), 170.2 (Cq, C=O); *m/z* (CI$^+$) 113.0602 (90%, MH$^+$, $C_6H_9O_2^+$ requires 113.0602).

(2*R*)-3-Methyl-2-{[(4-methylphenyl)sulfonyl]amino}butanoic acid (*N*-Ts-D-Val) 324



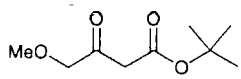
To a stirred suspension of D-valine (10.0 g, 85.0 mmol) in H_2O (100 mL) cooled 0 °C was added solid NaOH (3.50 g, 85.0 mmol) portionwise. *p*-toluenesulfonyl chloride (16.3 g, 85 mmol) was added, and the solution stirred at room temperature for 3h (during the course of the reaction, a pH of 9 was maintained by the addition of 10% NaOH solution). The reaction was then filtered and the filtrate acidified with 10% HCl solution to pH 5. Filtration gave **324** as white powder after drying (98%) analytical data was consistent with that reported.[236]

Butyl 2-methoxyacetate 325[237]



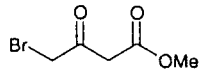
To a solution of pyridine (7.5 mL, 95.0 mmol), *n*-butanol (8.3 mL, 90.0 mmol) and dry DCM (100 mL) stirred at 0 °C under argon was added methoxyacetyl chloride (10.0 g, 90 mmol) dropwise. The mixture was refluxed for 1 hour then cooled to room temperature and filtered. The filtrate was washed with 5% HCl, brine, and finally water. After drying ($MgSO_4$) and concentration of the combined organic phases, pure **325** was obtained (11.3 g, 84 %) υ_{max} (neat)/cm^{-1} 3000 (strong, aliphatic C-H str.), 1760 (strong, C=O str.), 1480 (strong, C-H def.), 1190 (strong, 2 bands, C-O str.); δ_H (300 MHz) 0.90 (3H, t, *J* 6.9Hz, -CH_3), 1.35 (2H, m, -CH_2-), 1.65 (2H, m, -CH_2-), 3.45 (2H, s, -CH_2-), 3.97 (3H, s, -OCH_3), 4.15 (2H, t, *J* 6.9Hz, -CH_2-) ; δ_C (75.5 MHz) 13.7 (-CH_2CH_3), 19.2 (-CH_2CH_3), 31.2 ($CH_3CH_2CH_2$-), 59.3 (-OCH_3), 64.7 ($CH_3CH_2CH_2CH_2$-O), 69.7 (-CH_2OCH_3), 170.4 (Cq, C=O) *m/z* (CI$^+$) 164.2218 (M+NH_4, 100%, $C_{17}H_{18}NO_3^+$ requires 164.2230)

***tert*-Butyl 4-methoxy-3-oxobutanoate 327**



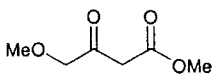
To a solution of dry diisopropylamine (6.5 mL, 47.3 mmol) in anhydrous THF (15 mL) stirred at 0 °C under argon was added *n*-BuLi (19.0 mL of a 2.5 mL solution in hexanes, 47.5 mmol) dropwise. The mixture was stirred for 0.5h, and the temperature reduced to -78 °C. Distilled *tert*-butyl acetate was added (5.8 mL, 43.0 mmol) dropwise and the reaction stirred for 10 minutes. Distilled methyl methoxyacetate (4.26 mL, 43.0 mmol) was added dropwise and the reaction stirred at -78 °C for 2h. The reaction was warmed to room temperature before quenching by the addition of 5% HCl (10 mL). After extracting into Et_2O and washing with 5% HCl (50 mL) and H_2O (50 mL), separation and concentration of the organic phase gave crude **327** that was distilled (95-100 °C, 0.5 mmHg) to yield pure **327** (6.21 g, 77%) ν_{max} (neat)/cm^{-1} 2979-2825 (several bands, medium, C-H. str.), 1748 (strong, C=O str. ester), 1726 (medium, C=O str. ketone), 1656 (weak, C=C str. enol), 1367 (strong, -C$(CH_3)_3$ C-H str.), 1152 (medium, C-O str.); δ_H (300 MHz) 1.42 (9H, s, 3x($\mathbf{CH_3}$)$_3$), 3.47 (2H, s, -$\mathbf{CH_2}$-), 3.48 (3H, s, -$\mathbf{OCH_3}$), 4.11 (2H, s, -$\mathbf{CH_2}$-); δ_C (100 MHz) 28.3 (($\mathbf{CH_3}$)$_3$), 47.5 (-$\mathbf{CH_2}$-), 59.7 (-$\mathbf{OCH_3}$), 81.5 (Cq, -$\mathbf{C}$(CH_3)$_3$), 75.7 (-$\mathbf{CH_2}$-), 166.5 (Cq, **C**=O ester), 202.3 (Cq, **C**=O ketone); *m/z* (FAB) 377 (10%, 2M+H^+), (ES$^+$) 189.1127 (100%, MH^+, $C_9H_{17}O_4^+$ requires 189.1127).

Methyl 4-bromo-3-oxobutanoate 328[238]



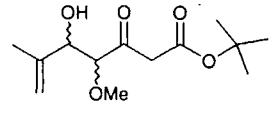
To a solution of methyl acetoacetate (18.6 mL, 170.0 mmol) in $CHCl_3$ (100.0mL), cooled to 0 °C and stirred under argon, was added Br_2 (8.8 mL, 160.0 mmol) as a solution in $CHCl_3$ (50.0 mL) dropwise. The reaction was stirred overnight at room temperature, and after this time air was passed through the solution for 2h. The remaining solvent was removed *in vacuo*, and the resulting liquid distilled (Kugelrohr 80 °C, 0.6 mmHg) to give **328** as a colourless oil (33.2 g, 98%) ν_{max}(neat)/cm^{-1} 1748 (strong, C=O str. ester), 1724 (medium, C=O str. ketone), 1633 (weak, C=C str. enol); δ_H (400 MHz) keto form 3.72 (2H, s, -$\mathbf{CH_2}$-), 3.79 (3H, s, -$\mathbf{OCH_3}$), 4.08 (2H, s, -$\mathbf{CH_2}$Br) enol form 3.81 (3H, s, -$\mathbf{OCH_3}$), 3.90 (2H, s, -$\mathbf{CH_2}$Br), 5.30 (1H, s, :**CH**); δ_C (100 MHz) keto form 34.4 (-$\mathbf{CH_2}$Br), 46.5 (-$\mathbf{CH_2}$-), 52.8 (-$\mathbf{OCH_3}$), 167.9 (Cq, **C**=O ester), 195.0 (Cq, **C**=O ketone) enol form 42.3 (-$\mathbf{CH_2}$Br), 52.1 (-$\mathbf{OCH_3}$), 92.2 (:**CH**), 167.0 (:**C**OH), 172.8 (Cq, **C**=O ester); *m/z* (CI$^+$) 211.9922 (M+NH_4^+, 100%, $C_5H_{11}BrO_3N^+$ requires 211.9922)

Methyl 4-methoxy-3-oxobutanoate 329[211]



To a boiling suspension of sodium methoxide (8.5 g, 160 mmol) in anhydrous THF (200 mL) was added bromoketoester **328** (10.0 g, 50 mmol) dropwise. After refluxing for 10 minutes, the reaction was cooled, neutralized with 20% HCl, filtered, and concentrated *in vacuo*. The residue was poured into water (150 mL) and extracted with DCM (100 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated to give a yellow oil that was purified by double distillation (85 °C, 0.3 mmHg) to give pure **329** as a pale yellow oil (5.04 g, 67%) ν_{max}(film)/cm^{-1} 1747 (strong, C=O str. ester), 1729 (medium, C=O str. ketone), 1657 (weak, C=O str. H-bonded enol chelate), 1633 (weak, C=C str. enol); δ_H (300 MHz) keto form 3.35 (3H, s, -OC**H**$_3$), 3.46 (2H, s, -C**H**$_2$-), 3.68 (3H, s, -OC**H**$_3$ ester), 4.05 (2H, s, -C**H**$_2$-) enol form 2.20 (1H, s, -O**H**, *exchanges with D_2O*), 3.41 (3H, s, -OC**H**$_3$), 3.70 (-OC**H**$_3$ ester), 3.91 (2H, s, -C**H**$_2$-), 5.19 (1H, s, :C**H**); δ_C (100 MHz) keto form 46.2 (-**C**H$_2$-), 52.7 (-O**C**H$_3$ ester), 59.5 (-O**C**H$_3$), 77.8 (-**C**H$_2$-), 167.8 (Cq, **C**=O), 202.0 (Cq, **C**=O ketone) enol form 51.7 (-O**C**H$_3$ ester), 61.8 (-O**C**H$_3$), 71.5 (-**C**H$_2$-) 103.9 (:**C**H), 174.3 (Cq, **C**=O ester) 184.27 (Cq, =**C**OH); *m/z* (CI$^+$) 164.0925 (100%, M+NH$_4^+$, $C_6H_{14}NO_4^+$ requires 164.0923)

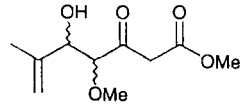
***tert*-Butyl 5-hydroxy-4-methoxy-6-methyl-3-oxo-6-heptenoate 330 via dienolate**



To a stirred solution of dry diisopropylamine (1.45 mL, 10.5 mmol) in anhydrous THF (20.0 mL) stirred at 0 °C under argon was added *n*-BuLi (4.3 mL of a 2.5M solution in hexanes, 10.8 mmol) dropwise. The reaction was stirred for 0.5h, and the temperature lowered to -78 °C. *Tert*-butyl 4-methoxy-3-oxobutanoate **327** (1.00 g, 5.28 mmol) was added dropwise and the reaction was stirred for 30 minutes. Methacrolein (0.46 mL, 5.28 mmol) was added dropwise and the reaction stirred at -78 °C for a further 2h. The reaction was warmed to room temperature, quenched by the addition of saturated $NaHCO_3$ (2 mL), diluted with Et_2O, and the organic layer separated. After washing with saturated $NaHCO_3$ (15 mL) and brine (15 mL), the combined organic phases were dried over $MgSO_4$ and concentrated to give a crude mixture of **330**. Purification by column chromatography (silica gel, 4:1 petroleum ether / ethyl acetate as eluant) gave pure **330** as the major product; pale yellow oil (1.05 g, 77%) ν_{max} (film)/cm^{-1} 3456 (b., O-H str.), 2979-2925 (several strong bands, C-H. str.), 1716 (strong, C=O str. ketone), 1649 (weak, C=C str. enol), 1367 (strong, -C(CH$_3$)$_3$ C-H str.), 1159 (2 bands, medium, C-O str.); δ_H (400 MHz) 1.45 (9H, s, 3x(C**H**$_3$)$_3$), 1.79 (3H, d, *J* 4.5Hz, :CH(C**H**$_3$)), 2.60 (1H, bs, -O**H**, *exchanges with D_2O*), 3.45 (2H, s, -C**H**$_2$-), 3.50 (3H, s, -OC**H**$_3$), 3.80 (1H,

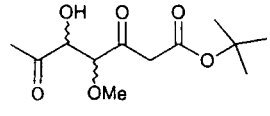
d, *J* 4.5Hz, -CH(OMe)), 4.31 (1H, d, *J* 4.5Hz, -CH(OH)), 5.05 (1H, d, *J* 8.1Hz, :CH), 5.09 (1H, d, *J* 8.1Hz, :CH); δ_C (100 MHz) 17.9 (:CH(CH_3), 26.9 (-C(CH_3)$_3$), 46.4 (-CH_2-), 58.9 (-OCH_3), 74.3 (-CH(OH)), 79.6 (Cq, -C(CH_3)$_3$), 86.8 (-HC(OCH_3), 112.0 (:CH_2), 142.4 (Cq, -C:CH_2), 165.7 (Cq, C=O ester), 204.0 (Cq, C=O ketone); *m/z* (FAB$^+$) 297 (MK$^+$, 100%), 259 (MH$^+$, 60%); (ES$^+$) 259.1544 (100%, MH$^+$, $C_{13}H_{23}O_5^+$ requires 259.1545).

Methyl 5-hydroxy-4-methoxy-6-methyl-3-oxo-6-heptenoate 331 via lithium dienolate



Prepared and purified by the procedure described above for **330**; pale yellow oil (72%) ν_{max}(neat)/cm^{-1} 3459 (b., O-H str.), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1650 (weak, C=C str. enol), 1188 (2 bands, medium, C-O str.); δ_H (300 MHz) 1.78 (3H, t, *J* 4.55Hz, :C(CH_3)), 2.85 (1H, bs, -OH *exchanges with D_2O*), 3.42 (2H, s, -CH_2-), 3.51 (3H, s, -OCH_3), 3.75 (3H, s, -OCH_3), 3.82 (1H, m, -CH(OCH_3)), 4.30 (1H, m, -CH(OH)-), 5.09 (1H, d, *J* 8.5Hz, :CH), 5.13 (1H, d, *J* 8.5Hz, :CH); δ_C (75.5 MHz) 17.9 (:CH(CH_3)), 45.4 (-CH_2-), 51.3 (-CO_2CH_3), 59.0 (-OCH_3), 73.1 (-CH(OH)), 86.7 (-CH(OCH_3)), 112.8 (:CH_2), 142.2 (:Cq), 166.8 (C=O ester, Cq), 203.7 (C=O ketone, Cq); *m/z* (ES$^+$) 217.1076 (100%, MH$^+$, $C_{10}H_{17}O_5^+$ requires 217.1076).

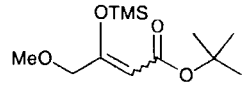
***tert*-Butyl 5-hydroxy-4-methoxy-3,6-dioxoheptanoate 332**



A solution of aldol adduct **330** (2.00 g) in dry DCM (15 mL) was cooled to -78 °C and saturated with O_3 (until the blue-purple colour persisted). Oxygen was then passed through the solution for a further 5 minutes, after which time anhydrous methyl sulfide (2mL) was added dropwise with stirring. The solution was then allowed to warm to room temperature, and was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 3:1 hexane / EtOAc as eluant) affording pure **332** (1.98 g, 98%); ν_{max}(neat)/cm^{-1} 3467 (b, strong, O-H str.), 2990-2919 (several strong bands, C-H str.), 1721 (strong, C=O str. ester), 1716 (strong, C=O str. ketone), 1651 (weak, C=C str. enol), 1365 (strong, -C(CH_3)$_3$, C-H str.), 1160 (2 bands, medium, C-O str.); δ_H (300 MHz) 1.49 (9H, s, 3 x -CH_3), 2.27 (3H, s, -CH_3), 2.72 (1H, bs, -OH, *exchanges with D_2O*), 3.335 (2H, s, -CH_2-), 3.54 (3H, s, -OCH_3), 4.18 (1H, m, -CH(OMe)), 4.52 (1H,

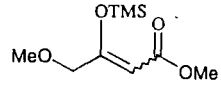
m, -CH(OH)); δ_C (75.5 MHz) 26.7 (-CH_3), 28.6 (-$C(CH_3)_3$), 48.0 (-CH_2-), 60.8 (-OCH_3), 77.4 (CH(OH)), 82.5 ($C(CH_3)_3$), 87.7 ($CH(OCH_3)$), 166.8 (C=O ester, Cq), 203.8 (C=O ketone, Cq), 206.2 (C=O ketone, Cq); *m/z* (ES^+) 278.1605 (100%, $(M+NH_4)^{+\cdot}$ $C_{12}H_{24}NO_6^+$ requires 278.1604.

4-(*tert*-Butoxy)-1-methoxy-4-[(trimethylsilyl)oxy]-3-buten-2-one 333



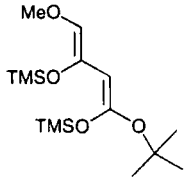
procedure followed as for **334**; distillation (Kugelrohr, 95-100 °C, 0.6 mmHg) gave **333** as a colourless oil (87%); ν_{max} (film)/cm^{-1} 1719 (strong, C=O str.), 1638 (medium, C=C str.), 1245 (medium, C-O str.), 846 (strong, $SiMe_3$); δ_H (300 MHz) *E* isomer: 0.014 (9H, s, -$SiCH_3$), 1.20 (9H, s, 2 x -CH_3), 3.10 (3H, s, -OCH_3), 4.18 (2H, s, -CH_2), 4.92 (1H, s, :CH) *Z* isomer: 0.02 (9H, s, -$Si(CH_3)_3$), 1.21 (9H, s, 3 x $C(CH_3)_3$), 3.11 (3H, s, -OCH_3), 3.49 (2H, s, -CH_2), 5.02 (1H, s, :CH) ; δ_C (75.5 MHz) 0.70 (-$Si(CH_3)_3$), 27.7 (3 x -CH_3), 58.7 (-OCH_3), 68.8 (-CH_2-), 78.5 (-$C(CH_3)_3$, Cq), 127.6 (:CH), 161.O (:C, Cq), 166.0 (C=O, Cq).

1,4-Dimethoxy-4-[(trimethylsilyl)oxy]-3-buten-2-one 334[211]



To a fine suspension of anhydrous zinc chloride (135.0 mg) in anhydrous Et_3N (10.3 mL, 74.0 mmol) was added methyl 4-methoxy-3-oxobutanoate **329** (5.00 g, 34.0 mmol) as a solution in anhydrous toluene (25 mL). The mixture was cooled to 0 °C, and TMS chloride (8.57 mL, 68.0 mmol) added slowly (2h). The reaction was stirred for 16h at 45 °C, and was then filtered, concentrated, and diluted with pet. ether (100 mL). After repeating this operation twice, the residue was distilled (Kugelrohr, 80-90 °C, 0.5 mmHg) to yield **334** as a pale yellow liquid (6.03 g, 81%); analytical data was consistent with that reported; δ_C (100 MHz) 0.4 (-$Si(CH_3)_3$), 50.3 (-OCH_3 ester), 58.1 (-CH_3), 73.1 (-CH_2-), 128.5 (:CH), 162.7 (:CH, Cq), 167.1 (C=O ester, Cq).

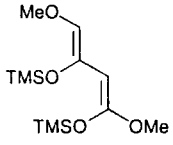
4-(*tert*-Butoxy)-2,4-bis[(trimethylsilyl)oxy]-1,3-butadienyl methyl ether 335



Procedure was carried out as for **336** above; yield typically 83%; pale yellow oil (Kugelrohr, 115-125 °C, 0.5 mmHg); ν_{max} (film)/cm^{-1} 1677 (strong, C=C str. enol ether), 1617 (strong, C=C str. conj), 1367 (strong, -$C(CH_3)_3$ C-H str.), 1248 (strong,

$SiMe_3$), 1215 (medium, C-O str.), 844 (strong, $SiMe_3$); major isomer: δ_H (300 MHz) 0.27 (9H, s, -Si(CH_3)$_3$), 0.33 (9H, s, -Si(CH_3)$_3$), 1.41 (9H, s, -C(CH_3)$_3$), 3.48 (3H, s, -OCH_3), 4.83 (1H, s, :CH),5.70 (1H, s, :CH); δ_C (75.5 MHz) -0.60 (-Si(CH_3)$_3$), 0.3 (-Si(CH_3)$_3$), 27.8 (C(CH_3)$_3$), 59.3 (-CH_3), 78.5 (C(CH_3)$_3$), 84.2 (:CH), 100.5 (:CH), 132.9 (:CH, Cq), 150.8 (:CH, Cq). *NB*: Due to the instablility of **335** and **336**, a thorough analysis could not be obtained.

1,4-Dimethoxy-3-[(trimethylsilyl)oxy]-1,3-butadienyl trimethylsilyl ether 336[211]



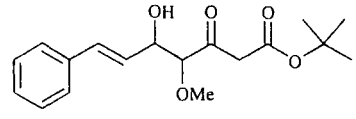
To a solution of diisopropylamine (2.23 mL, 11.0 mmol) in dry THF (20 mL) cooled to 0 °C and stirred under argon was added *n*-BuLi (4.8 mL of a 2.6M solution in hexanes, 11.5 mmol) dropwise. After stirring for 0.5h, the temperature was reduced to -78 °C. A solution of **334** (2.5 g, 11.0 mmol) in dry THF (5 mL) was added over 2h, followed by TMS-Cl (1.45 mL, 11 mmol) over 2h. After stirring for 0.5h, the solution was allowed to warm to room temperature and was concentrated *in vacuo*. The residue was treated with pet. ether (30 mL) and filtered. After repeating this operation, the residue was distilled (Kugelrohr, 75-85 °C, 0.6 mmHg) to give **336** as a pale yellow liquid (72%). Analytical data obtained was in accord with that published; δ_C (75.5MHz) -0.6 (-Si(CH_3)$_3$), 0.3 (-Si(CH_3)$_3$), 27.8 (C(CH_3)$_3$), 59.3 (-CH_3), 78.5 (C(CH_3)$_3$), Cq), 84.2 (:CH), 100.5 (:CH), 132.9 (:CH, Cq), 150.8 (:CH, Cq).

Typical procedure for the oxazaborolidine promoted asymmetric aldol reaction

To a solution of N-Ts-D-valine **324** (0.20 g, 25 mol %, 0.75 mmol) in dry DCM (10mL) was added BH_3 (0.75 mL of a 1.0M solution in THF, 25 mol %, 0.75 mmol) dropwise over 0.5h. The mixture was stirred for a further 0.5h, and the temperature lowered to -78 °C. Methacrolein (0.26 mL, 3.00 mmol) was added dropwise, followed by a solution of **335** (1.00 g, 3.00 mmol) in dry DCM (5 mL). The reaction was stirred for 6h at -78 °C then warmed to room temperature and stirred for a further 16h. After this time, saturated $NaHCO_3$ (3 mL) was added and the reaction stirred for a further 0.5h. The reaction mixture was diluted with DCM (20 mL), and the organic layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was treated with cold hexane and filtered to recover the N-Ts-D-valine (with typically 90% recovery). The solution was re-concentrated *in vacuo*, and the residue diluted with THF (25 mL), cooled to 0 °C, and treated dropwise with a 10% aqueous solution of TFA (5 mL). After stirring for 2h, the solution was warmed to room temperature and

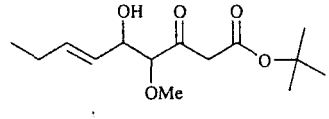
partitioned between Et_2O and H_2O. The organic layer was washed with saturated $NaHCO_3$ solution (20 mL) and finally brine (20 mL), before being dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica gel, 4:1 hexane / EtOAc as eluant) gave the aldol product as the major component (0.59 g, 76%); analytical data was consistent with that obtained for **330**. Yield from 1,4-dimethoxy-3-[(trimethylsilyl)oxy]-1,3-butadienyl trimethylsilyl ether **336** 0.49 g (66%); analytical data consistent with that obtained for **331**.

***tert*-Butyl (*E*)-5-hydroxy-4-methoxy-3-oxo-7-phenyl-6-heptenoate 337**



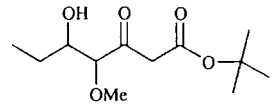
obtained from 0.75 mmol of diene **335**: bright yellow oil (215 mg, 90%); ν_{max}(film)/cm^{-1} 3450 (b, O-H str.), 3025-3009 (medium, several bands, C-H str.), 1715 (strong, C=O str.), 1600 and 1515 (strong, C=C str.), 1365 (strong, -C(CH$_3$)$_3$ C-H str.), 1160 (strong, C-O str.); δ_H (400MHz) 1.39 (9H, s, -C(**CH**$_3$)$_3$), 2.82 (1H, bs, -**OH**, *exchanges with D$_2$O*), 3.42 (2H, s, -**CH**$_2$-), 3.51 (3H, s, -**OMe**), 3.72 (1H, m, -**CH**(OMe), 4.65 (1H, m, -**CH**(OH)), 6.18 (1H, m, :**CH**), 6.62 (1H, d, *J* 14.7Hz, :**CH**), 7.23-7.31 (5H, m, ArH); δ_C (100 MHz) 28.4 (-C(**CH**$_3$)$_3$), 47.8 (-**CH**$_2$-), 59.8 (-**OCH**$_3$), 73.3(-**CH**(OH)), 82.3 (-**C**(CH$_3$)$_3$), 89.6 (-**CH**(OCH$_3$)), 126.6 (Ar**C**), 126.9 (Ar**C**), 127.6 (Ar**C**), 128.9 (Ar**C**), 129.4 (Ar**C**), 136.5 (Cq, Ar**C**), 166.3 (Cq, **C**=O ester), 204.2 (Cq, **C**=O ketone); *m/z* (ES$^+$) 343.1519 (100%, M+Na$^+$, $C_{18}H_{24}O_5Na^+$ requires 343.1522)

***tert*-Butyl (*E*)-5-hydroxy-4-methoxy-3-oxo-6-nonenoate 338**



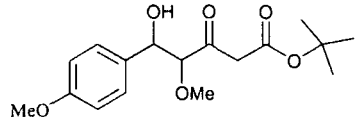
obtained from 0.75 mmol of diene **335**: light yellow oil (151 mg, 77%); ν_{max}(film)/cm^{-1} 3466 (b., O-H str.), 2787 (several strong bands, C-H str.), 1720 (strong, C=O str. ketone), 1646 and 1620 (weak, C=C str.), 1362 (strong, -C(CH$_3$)$_3$ C-H str.), 1185 (2 bands, medium, C-O str.); δ_H (300 MHz) 0.96 (3H, t, *J* 7.1Hz, -**CH**$_3$), 1.45 (9H, bs, -C(**CH**$_3$)$_3$), 1.99 (2H, m, -**CH**$_2$CH$_3$), 2.83 (1H, bs, -**OH**), 3.45 (2H, s, -**CH**$_2$-), 3.51 (3H, s, -**OCH**$_3$), 3.81 (1H, m, -**CH**(OMe)), 4.46 (1H, m, -**CH**(OH)), 5.45 (1H, dd, *J* 16.9, 7.1Hz, :**CH**), 6.03 (1H, td, *J* 6.6, 16.9Hz, :**CH**); δ_C (75.5 MHz) 14.5 (-**CH**$_3$), 24.6 (-**CH**$_2$CH$_3$), 26.8 (-C(**CH**$_3$)$_3$), 46.5 (-**CH**$_2$-), 59.7 (-**OCH**$_3$), 73.4 (-**CH**(OH)), 80.6 (-**C**(CH$_3$)$_3$), 86.7 (-**C**(OMe)), 131.6 (:**CH**), 136.1 (:**CH**), 166.5 (Cq, **C**=O ester), 203.8 (Cq, **C**=O ketone); *m/z* (ES$^+$) 273.1705 (100%, MH$^+$, $C_{14}H_{25}O_5^+$ requires 273.1702).

***tert*-Butyl 5-hydroxy-4-methoxy-3-oxoheptanoate 339**



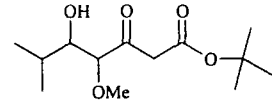
obtained from 0.75 mmol of diene **335**: light yellow oil (127 mg, 72%); ν_{max}(film)/cm^{-1} 3457 (b., O-H str.), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1650 (weak, C=C str. enol), 1365 (strong, -C(CH$_3$)$_3$ C-H str.), 1188 (2 bands, medium, C-O str.); δ_H (400 MHz) 0.97 (3H, t, *J* 6.9Hz, -CH$_3$), 1.47 (9H, bs, -C(CH$_3$)$_3$), 1.55 (2H, m, -CH$_2$CH$_3$), 2.87 (1H, bs, -OH *exchanges with D$_2$O*), 3.48 (2H, s, -CH$_2$-), 3.52 (3H, s, -CH$_3$), 3.77 (1H, m, -CH(OMe)), 4.33 (1H, m, -CH(OH)); δ_C (100 MHz) 10.8 (-CH$_3$), 26.8 (-CH$_2$CH$_3$), 27.8 (-C(CH$_3$)$_3$), 47.1 (-CH$_2$-), 59.9 (-OCH$_3$), 74.7 (-CH(OH)), 80.1 (-C(CH$_3$)$_3$), 86.9 (-CH(OMe)), 166.6 (Cq, C=O ester), 203.9 (Cq, C=O ketone); *m/z* (CI$^+$) 264.1810 (100%, M+NH$_4^+$, $C_{12}H_{26}NO_5^+$ requires 264.1811)

***tert*-Butyl 5-hydroxy-4-methoxy-5-(4-methoxyphenyl)-3-oxopentanoate 340**



obtained from 0.75 mmol of diene **335**: light yellow oil (183 mg, 78%); ν_{max}(film)/cm^{-1} 3450 (b., O-H str.), 3040-3025 (medium, Ar-H str.aromatic), 1733 (strong, C=O str. ketone), 1656 (weak, C=C str. enol), 1369 (strong, -C(CH$_3$)$_3$ C-H str.), 1168 (2 bands, medium, C-O str.); δ_H (500MHz) 1.48 (9H, s, -C(CH$_3$)$_3$), 2.77 (1H, bs, -OH *exchanges with D$_2$O*), 3.49 (2H, s, -CH$_2$-), 3.52 (3H, s, -OCH$_3$), 3.80 (3H, s, ArOCH$_3$), 3.91 (1H, m, -CH(OMe)), 4.66 (CH(OH)), 6.88 (2H, d, *J* 8.1Hz, ArH), 7.08 (2H, d, *J* 8.1Hz, ArH); δ_C (75.5 MHz) 27.1 (-C(CH3)$_3$), 46.9 (-CH$_2$-), 56.1 (Ar-OCH$_3$), 77.3 (-CH(OH)), 80.8 (Cq, -C(CH$_3$)$_3$), 89.1 (-CH(OMe)), 114.6 (ArC), 129.6 (ArC), 139.3 (Cq, ArC), 158.7 (Cq, ArC), 165.0 (Cq, C=O ester), 205.0 (Cq, C=O ketone); *m/z* (ES$^+$) 347.1469 (100%, M+Na$^+$, $C_{17}H_{24}O_6Na^+$ requires 347.1471)

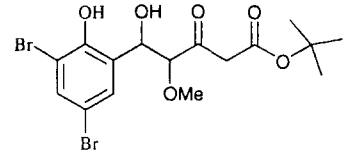
***tert*-Butyl 5-hydroxy-4-methoxy-6-methyl-3-oxoheptanoate 341**



obtained from 0.75 mmol of diene **335**: pale yellow oil (126 mg, 67%); ν_{max}(film)/cm^{-1} 3459 (br., O-H str.), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1654 (weak, C=C str. enol), 1365 (strong, -C(CH$_3$)$_3$ C-H str.), 1188 (2 bands, medium, C-O str.); δ_H (300 MHz) 0.89 (3H, s, -CH$_3$), 0.92 (3H, s, -CH$_3$), 1.39 (9H, bs, C(CH$_3$)$_3$), 2.19 (1H, m, -CH), 2.58 (1H, bs, -OH, *exchanges with D$_2$O*), 3.39 (2H, s, -CH$_2$-), 3.41 (3H, s, -OCH$_3$), 3.83 (1H, m, -CH(OMe)), 4.21 (1H, m, -CH(OH)); δ_C

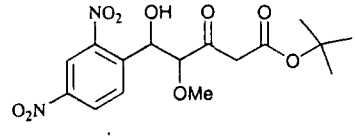
(75.5 MHz) 18.4 (-CH_3), 20.7 (-CH_3), 27.8 ($C(CH_3)_3$), 30.2 (CH), 46.6 (-CH_2-), 60.1 (-OCH_3), 71.2 (CH(OH)), 82.2 (Cq, -$C(CH_3)_2$), 85.9 (CH(OMe)), 165.6 (Cq, C=O ester), 202.2 (Cq, C=O ketone); *m/z* (ES^+) 283.1520 (100%, $M+Na^+$, $C_{13}H_{24}O_5Na^+$ requires 283.1522)

***tert*-Butyl 5-(3,5-dibromo-2-hydroxyphenyl)-5-hydroxy-4-methoxy-3-oxopentanoate 342**



obtained from 0.75 mmol of diene **335**: yellow oil (270 mg, 80%); ν_{max}(film)/cm^{-1} 3459 (b., O-H str.), 3035 (weak, Ar-H str.), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1652 (weak, C=C str. enol), 1365 (strong, -$C(CH_3)_3$,C-H str.), 1175 (2 bands, medium, C-O str.); δ_H (300 Hz) 1.42 (9H, bs, -$C(CH_3)_3$), 2.61 (1H, bs, -OH *exchanges with D_2O*), 3.40 (2H, s, -CH_2-), 3.54 (3H, s, -OCH_3), 4.00 (1H, m, CH(OCH_3)), 4.92 (1H, s, Ar-OH, *exchanges with D_2O*), 5.79 (1H, m, CH(OH)), 7.59 (1H, d, *J* 2.4Hz, ArH), 7.82 (1H, d, *J* 2.4Hz, ArH); δ_C (75.5 Hz) 28.6 (-$C(CH_3)_3$), 46.2 (-CH_2-), 58.3 (-OCH_3), 63.8 (-CH(OH)), 79.7 (Cq, $C(CH_3)_3$), 89.3 (CH(OCH_3), 111.4 (Cq, ArC), 120.8 (Cq, ArC), 128.6 (Cq, ArC), 132.1 (Cq, ArC), 133.64 (ArC), 156.2 (Cq, ArC), 165.2 (Cq, C=O ester), 200.9 (Cq, C=O ketone); *m/z* (ES^+) 490.9509 (100%, $M+Na^+$, $C_{16}H_{20}Br_2O_6Na^+$ requires 490.9504)

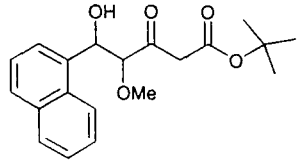
***tert*-Butyl 5-(2,4-dinitrophenyl)-5-hydroxy-4-methoxy-3-oxopentanoate 343**



obtained from 0.75 mmol of diene **335**: yellow oil (244 mg, 88%); ν_{max}(film)/cm^{-1} 3459 (b., O-H str.), 3034-3015 (several bands, medium, Ar-H str.aromatic), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1635 (weak, C=C str. enol), 1525 (strong, N-O str.), 1365 (strong, -$C(CH_3)_3$ C-H str.), 1355 (2 bands, strong, N-O asymm. and symm. str.), 1177 (2 bands, medium, C-O str.); δ_H (300 Hz) 1.44 (9H, s, -$C(CH_3)_3$), 2.89 (1H, bs, -OH *exchanges with D_2O*), 3.49 (2H, s, -CH_2-), 3.54 (3H, s, -OCH_3), 4.10 (1H, m, -CH(OCH_3)), 5.90 (1H, m, -CH(OH)), 8.09 (1H, d, *J* 8.1Hz, ArH), 8.4 (1H, dd, *J* 8.1, 2.0Hz, ArH), 8.77 (1H, d, *J* 2.0Hz, ArH); δ_C (75.5 Hz) 28.2 (-$C(CH_3)_3$), 47.4 (-CH_2-), 59.4 (-OCH_3), 68.9 (-CH(OH)), 82.9 (Cq, $C(CH_3)_3$), 87.9 (CH(OCH_3)), 120.1 (ArC), 127.4 (ArC), 131.1 (ArC), 147.4 (Cq, ArC), 143.3 (Cq,

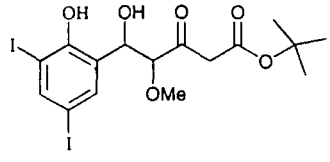
ArC), 147.5 (Cq, ArC), 167.3 (Cq, C=O ester), 204.2 (Cq, C=O ketone); *m/z* (ES^+) 385.1168 (100%, MH^+, $C_{16}H_{21}N_2O_9^+$ requires 385.1169).

***tert*-Butyl 5-hydroxy-4-methoxy-5-(1-naphthyl)-3-oxopentanoate 344**



obtained from 0.75 mol of diene **335**: pale yellow oil (179 g, 72%); ν_{max}(film)/cm^{-1} 3459 (br., O-H str.), 3055-3035 (several bands, medium, Ar-H str.aromatic), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1650 (weak, C=C str. enol), 1365 (strong, $-C(CH_3)_3$ C-H str.), 1180 (2 bands, medium, C-O str.); δ_H (300 Hz) 1.39 (9H, s, $-C(CH_3)_3$), 2.78 (1H, bs, -OH *exchanges with D_2O*), 3.39 (2H, s, $-CH_2-$), 3.49 (3H, s, $-OCH_3$), 3.92 (1H, m, $-CH(OCH_3)$), 5.86 (1H, m, -CH(OH)), 6.91-8.16 (7H, m, ArH); δ_C (75.5 Hz) 27.7 ($-CH_3$), 46.7 ($-CH_2-$), 58.3 ($-OCH_3$), 72.3 (CH(OH)), 80.8 (Cq, $C(CH_3)_3$), 87.8 (CH(OMe)), 122.8 (ArC), 125.2 (ArC), 125.4 (ArC), 126.2 (ArC), 126.7 (ArC), 129.3 (ArC), 129.9 (Cq, ArC), 130.3 (ArC), 133.1 (Cq, ArC), 145.7 (Cq, ArC), 167.3 (Cq, C=O ester), 202.9 (Cq, C=O ketone); *m/z* (CI^+) 338.2342 (100%, $M+NH_4^+$, $C_{20}H_{28}NO_5^+$ requires 338.2345)

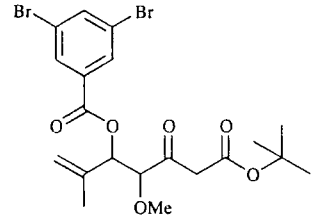
***tert*-Butyl 5-hydroxy-5-(2-hydroxy-3,5-diiodophenyl)-4-methoxy-3-oxopentanoate 345**



obtained from 0.75 mol of diene **335**: light yellow oil (337 g, 83%); ν_{max}(film)/cm^{-1} 3469 (b., O-H str.), 3038-3012 (several bands, medium, Ar-H str.), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1647 (weak, C=C str. enol), 1365 (strong, $-C(CH_3)_3$ C-H str.), 1175 (2 bands, medium, C-O str.); δ_H (500 Hz) 1.45 (9H, s, $-C(CH_3)_3$), 2.58 (1H, bs, -OH *exchanges with D_2O*), 3.44 (2H, s, $-CH_2-$), 3.52 (3H, s, $-OCH_3$), 3.97 (1H, m, -CH(OMe)), 4.79 (1H, bs, Ar-OH *exchanges with D_2O*), 5.81 (1H, m, -CH(OH)), 7.48 (1H, d, *J* 2.0Hz, ArH), 7.80 (1H, d, *J* 2.0Hz, ArH); δ_C (125.5MHz) 29.1 ($-C(CH_3)_3$), 47.2 ($-CH_2-$), 58.8 ($-OCH_3$), 64.5 (-CH(OH)), 80.1 (Cq, $-C(CH_3)_3$), 88.7 ($CH(OCH_3)$), 113.5 (Cq, ArC), 131.6 (Cq, ArC), 137.8 (ArC), 147.9 (ArC), 157.3

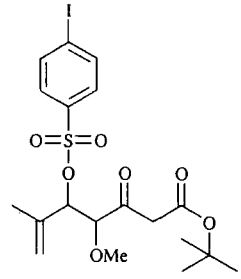
(Cq, ArC), 166.6 (Cq, C=O ester), 201.0 (Cq, C=O ketone); *m/z* (ES^+) 585.9454 (100%, $M+Na^+$, $C_{17}H_{22}I_2O_5Na^+$ requires 585.9455)

1-[4-(*tert*-Butoxy)-1-methoxy-2,4-dioxobutyl]-2-methyl-2-propenyl-3,5-dibromobenzoate 348



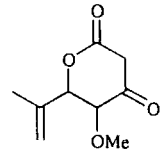
To a stirred suspension of sodium hydride (10.0 mg, 1.08 eq) in anhydrous THF (10 mL) cooled to 0 °C and stirred under Ar was added solution of aldol **330** (100.0 mg, 0.387 mmol) in anhydrous THF (2 mL) dropwise. A solution of 3,4-dibrombenzoyl chloride (116.9 mg, 1.0 eq) in anhydrous THF (2 mL) was added dropwise, and the reaction stirred at 0 °C and monitored by TLC. After 2h the reaction was quenched by the addition of 1% HCl and extracted into Et_2O. The organic phase was washed with 1% HCl (2 x 10mL) and brine (20mL), and dried over $MgSO_4$. Concentration *in vacuo* gave a yellow oil that was purified by silica gel chromatography (eluting with 4:1 hexane / EtOAc) to give **348** (78 mg, 68%); ν_{max}(film)/cm^{-1} 3040-3020 (several bands, weak, Ar-H str.), 2790 (several strong bands, C-H str.), 1720 (strong, C=O str. ketone), 1642 (weak, C=C str. enol), 1366 (strong, $-C(CH_3)_3$ C-H str.), 1169 (2 bands, medium, C-O str.); δ_H (400 MHz) 1.44 (9H, s, $C(CH_3)_3$), 1.71 (3H, d, *J* 4.5Hz, $-CH_3$), 3.38 (2H, s, $-CH_2-$), 3.53 (3H, s, $-OCH_3$), 4.24 (1H, m, $CH(OCH_3)$), 5.01 (1H, d, *J* 8.1Hz, :CH), 5.05 (1H, d, *J* 8.1Hz, :CH), 5.82 (1H, m, $CH(CO_2Ar)$, 7.38 (1H, d, *J* 2.2Hz, ArH), 8.11 (2H, d, *J* 2.2Hz, ArH); δ_C (100 MHz) 17.8 ($-CH_3$), 26.9 ($-C(CH_3)_3$), 46.6 ($-CH_2-$), 59.8 ($-OCH_3$), 77.1 ($CH(O_2C)$), 81.2 (Cq, $C(CH_3)_3$), 85.5 ($CH(OCH_3)$), 114.4 ($:CH_2$), 124.8 (ArC), 129.1 (Cq, ArC), 131.2 (ArC), 133.1 (Cq, ArC), 140.9 (Cq, C:CH_2), 163.8 (Cq, C=O ester), 166.5 (Cq, C=O ester), 203.4 (Cq, C=O ketone); *m/z* (ES^+) 520.9994 (100%, MH^+, $C_{20}H_{25}Br_2O_6^+$ requires 520.9998)

***tert*-Butyl 5-{[(4-iodophenyl)sulfonyl]oxy}-4-methoxy-6-methyl-3-oxo-6-heptenoate 349**



To a solution of aldol **330** (50.0 mg, 0.192 mmol) in dry DCM (2 mL) cooled to 0 °C and stirred under Ar was added pyridine (22 μL, 1.1 eq) followed by a solution of 4-iodobenzenesulfonyl chloride (59.0 mg, 1 eq) in dry DCM (1 mL) dropwise. The reaction was warmed to RT and stirred overnight. After this time the reaction was diluted with DCM (5 mL) and the organic phase washed with 5% HCl (10 mL) and brine (2 x 10 mL). The combined organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil; purification by silica gel chromatography (1:1 hexane / Et_2O as eluant) gave **349** as a light yellow oil (57 mg, 56%); ν_{max}(film)/cm^{-1} 3045-3027 (several bands, medium, Ar-H str.aromatic), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1645 (weak, C=C str. enol), 1365 (strong, -C(CH_3)$_3$ C-H str.)1188 (2 bands, medium, C-O str.); δ_H (400 MHz) 1.44 (9H, s, -C(**C**H_3)$_3$), 1.80 (3H, d, *J* 4.4Hz, :CH(**C**H_3)), 3.48 (2H, s, -**C**H_2-), 3.51 (3H, s, -O**C**H_3), 4.02 (1H, m, -**C**H(OCH_3)), 4.64 (1H, m, -**C**H(OSO_2Ar)), 5.04 (1H, d, *J* 8.3Hz, :**C**H), 5.11 (1H, d, *J* 8.3Hz, :**C**H), 7.66 (2H, d, *J* 7.8Hz, Ar**H**), 7.99 (2H, d, *J* 7.8Hz, Ar**H**); δ_C (100 MHz) 19.7 (-**C**H_3), 27.0 (-(**C**H_3)$_3$), 46.5 (-**C**H_2-), 58.9 (-O**C**H_3), 81.1 (Cq, **C**(CH_3)$_3$), 85.5 (**C**H(OH)), 86.8 (**C**H(OCH_3)), 97.9 (Cq, Ar**C**), 113.0 (:**C**H_2), 128.3 (Ar**C**), 135.9 (Ar**C**), 141.8 (Cq, :**C**(CH_2), 148.2 (Cq, Ar**C**), 167.7 (Cq, **C**=O ester), 203.9 (Cq, **C**=O ketone); *m/z* (ES$^+$) 547.3640 (100%, M+Na$^+$, $C_{19}H_{25}IO_7SNa^+$ requires 547.3643)

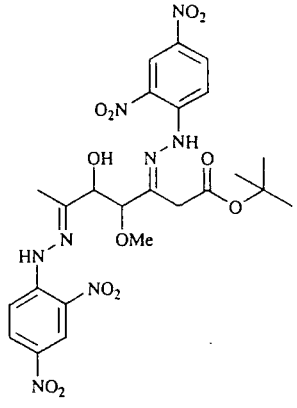
6-Isopropenyl-5-methoxydihydro-2*H*-pyran-2,4(3*H*)-dione 352



To a solution of aldol **330** (50.0 mg, 0.194 mmol) in dry DCM (2 mL) cooled to 0 °C and stirred under Ar was added TFA (98 μL, 7 eq). The reaction was stirred at RT for 3h, after which time solid $NaHCO_3$ was added to quench. The mixture was extracted into EtOAc and washed with water to pH 7. After drying over $MgSO_4$, concentration *in vacuo* gave a brown oil that was passed through a short silica column using 5:1 hexane / EtOAc as eluant. Gave **352** as a minor fraction; (11 mg, 33%); ν_{max}(film)/cm^{-1} 1754

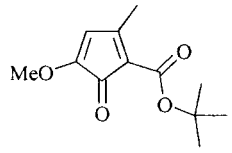
(strong, C=O str.); δ_H (500 MHz) 1.81 (3H, d, *J* 4.6Hz, -CH_3), 3.22 (2H, m, -CH_2-), 3.49 (3H, s, -OCH_3), 3.89 (1H, m, -CH), 4.98 (1H, d, *J* 7.7Hz, :CH), 5.03 (1H, d, *J* 7.7Hz, :CH), 5.11 (1H, m, CH); δ_C (125.5 MHz) 18.6 (:CH(CH_3)), 45.1 (-CH_2-), 59.1 (-OCH_3), 78.7 (CH), 85.6 (CH), 116.9 (:CH_2), 140.8 (Cq, C(CH_2)), 166.7 (Cq, C=O ester), 209.1 (Cq, C=O ketone); *m/z* (ES^+) 207.0629 (100%, M+Na^+, $C_9H_{12}O_4Na^+$ requires 207.06233)

<u>*tert*-Butyl(4*R*,5*R*)-6-[(*E*)-2-(2,4-dinitrophenyl)hydrazono]-3-[(*Z*)-2-(2,4-dinitrophenyl)hydrazono]-5-hydroxy-4-methoxyheptanoate 354</u>



To a solution of 2,4-dinitrophenylhydrazine (140.0 mg, 2.2 eq of a 35% water-moistened solid) in EtOH stirred at RT under Ar was added dione **332** (50.0 mg, 0.192 mmol). After stirring overnight, the reaction was concentrated *in vacuo* to give a bright orange oil that was subjected to silica gel chromatography (3:1 hexane / EtOAc as eluant). Minor (second) fraction: yellow oil (42.7 mg, 36%) that was best stored at -18 °C under Ar; ν_{max}(film)/cm^{-1} 3519 (b., O-H str.), 3395 (medium, N-H imine), 3053-3038 (several bands, medium, Ar-H str.aromatic), 2790 (several strong bands, C-H str.), 1725 (strong, C=O str. ketone), 1525 (strong, N-O str.), 1687 (strong, C=N str.), 1365 (strong, -C(CH_3)$_3$ C-H str.) 1355 (2 bands, strong, N-O asymm. and symm. str.), 1188 (2 bands, weak, C-O str.); δ_H (400 MHz) 1.40 (9H, s, C(CH_3)$_3$), 1.92 (3H, s, -CH_3), 2.91 (1H, bs,-OH, *exchanges with D_2O*), 3.33 (3H, s, -OCH_3), 3.49 (2H, s, -CH_2), 4.91 (1H, m, -CH(OCH_3)), 5.29 (1H, m, -CH(OH)), 7.81-7.97 (4H, d, *J* 8.9Hz, ArH), 8.78 (2H, d, *J* 2.3Hz, ArH), 8.91 (2H, bs, -NH) ; δ_C (100 MHz) 15.1 (-CH_3), 27.8 (b, C(CH_3)$_3$), 39.5 (-CH_2-), 56.9 (-OCH_3), 70.1 (CH(OH)), 74.2 (CH(OCH_3)), 82.5 (Cq, C(CH_3)$_3$), 105.6 (ArC), 123.9 (ArC), 131.3 (ArC), 131.5 (ArC), 138.1 (Cq, ArC), 138.8 (Cq, ArC), 139.1 (Cq, ArC), 139.4 (Cq, ArC), 144.8 (Cq, C=N), 145.1 (Cq, C=N), 145.9 (Cq, ArC), 146.7 (Cq, ArC), 169.9 (Cq, C=O ester); *m/z* (CI^+) 638.56 (100%, M+NH_4^+)

<u>*tert*-Butyl 4-methoxy-2-methyl-5-oxo-1,3-cyclopentadiene-1-carboxylate 355</u>



To a solution of dione **332** (50.0 mg, 19.2 mmol) in dry MeOH (2mL) cooled to 0 °C and stired under Ar was added K_2CO_3 (53.0 mg, 2 eq). After stirring for 5h at 0 °C, the reaction was quenched by the addition of water (2 mL) and extracted with Et_2O (10 mL). The organic phases were washed with brine, concentrated *in vacuo*, and dried over $MgSO_4$ to give a dark brown solid (105 mg); mixture could not be separated by column chromatography. Analytical data for principal component: ν_{max}(film)/cm^{-1} 1685 (strong, C=O str.), 1610 (strong, C=C str.); δ_H (400 MHz) 1.48 (9H, s, 3 x CH3), 2.19 (3H, s, -C**H**$_3$), 3.68 (3H, s, OC**H**$_3$), 7.36 (1H, s, :C**H**); δ_C (100 MHz) 20.6 (-**C**H_3), 28.8 (3 x -**C**H_3), 56.1 (-O**C**H_3), 82.1 (**C**$(CH_3)_3$), 130.9 (Cq, :**C**H$(CO_2C(CH_3)_3)$), 145.5 (:**C**H), 153.9 (Cq, **C**(OCH_3)), 163.5 (Cq, **C**=O ester), 171.1 (Cq, **C**(CH_3)), 180.5 (Cq, **C**=O ketone); *m/z* (CI^+) 200.1 (100%, M+NH_4^+).

Appendix A: Crystallographic data

Table 1. Crystal data and structure refinement for **255**

Empirical formula	$C_{20}H_{16}N$	
Formula weight	270.34	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 10.013(3) Å	α= 90°.
	b = 10.770(3) Å	β= 94.151(16)°.
	c = 13.828(2) Å	γ = 90°.
Volume	1487.3(6) $Å^3$	
Z	4	
Density (calculated)	1.207 Mg/m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	572	
Crystal size	0.40 x 0.30 x 0.30 mm^3	
Theta range for data collection	2.04 to 24.97°.	
Index ranges	-11<=h<=2, 0<=k<=12, -16<=l<=16	
Reflections collected	3379	
Independent reflections	2613 [R(int) = 0.0221]	
Completeness to theta = 24.97°	100.0 %	
Max. and min. transmission	0.9794 and 0.9726	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2613 / 0 / 254	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0456, wR2 = 0.0873	
R indices (all data)	R1 = 0.0921, wR2 = 0.1037	
Largest diff. peak and hole	0.125 and -0.156 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **255**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(8)	5802(2)	1403(1)	532(1)	33(1)
C(1)	7468(2)	2598(2)	1397(1)	31(1)
C(2)	8217(2)	2862(2)	2251(2)	42(1)
C(3)	9140(2)	3817(2)	2295(2)	49(1)
C(4)	9305(2)	4531(2)	1491(2)	46(1)
C(5)	8558(2)	4282(2)	643(2)	42(1)
C(6)	7652(2)	3327(2)	589(2)	37(1)
C(7)	6458(2)	1588(2)	1345(1)	29(1)
C(9)	4805(2)	417(2)	418(1)	32(1)
C(10)	3442(2)	987(2)	202(1)	36(1)
C(11)	3231(3)	1837(2)	-544(2)	45(1)
C(12)	1987(3)	2347(2)	-759(2)	61(1)
C(13)	942(3)	2030(3)	-233(2)	69(1)
C(14)	1132(3)	1204(3)	513(2)	69(1)
C(15)	2380(2)	673(2)	736(2)	55(1)
C(16)	6248(2)	859(2)	2239(1)	30(1)
C(17)	5106(2)	1046(2)	2729(1)	39(1)
C(18)	4854(3)	311(2)	3506(2)	46(1)
C(19)	5724(3)	-607(2)	3808(2)	48(1)
C(20)	6874(3)	-793(2)	3342(2)	47(1)
C(21)	7135(2)	-60(2)	2560(2)	39(1)

Table 3. Bond lengths [Å] and angles [°] for **255**.

N(8)-C(7)	1.276(2)
N(8)-C(9)	1.458(2)
C(1)-C(2)	1.382(3)
C(1)-C(6)	1.389(3)
C(1)-C(7)	1.484(3)
C(2)-C(3)	1.381(3)
C(3)-C(4)	1.372(3)
C(4)-C(5)	1.371(3)
C(5)-C(6)	1.370(3)
C(7)-C(16)	1.492(3)
C(9)-C(10)	1.506(3)
C(9)-C(9)#1	1.537(4)
C(10)-C(15)	1.380(3)
C(10)-C(11)	1.384(3)
C(11)-C(12)	1.374(3)
C(12)-C(13)	1.360(4)
C(13)-C(14)	1.365(4)
C(14)-C(15)	1.388(4)
C(16)-C(21)	1.381(3)
C(16)-C(17)	1.385(3)
C(17)-C(18)	1.372(3)
C(18)-C(19)	1.364(3)
C(19)-C(20)	1.373(3)
C(20)-C(21)	1.380(3)
C(7)-N(8)-C(9)	120.88(16)
C(2)-C(1)-C(6)	118.42(19)
C(2)-C(1)-C(7)	121.23(18)
C(6)-C(1)-C(7)	120.32(17)
C(3)-C(2)-C(1)	120.7(2)
C(4)-C(3)-C(2)	120.1(2)
C(5)-C(4)-C(3)	119.6(2)
C(6)-C(5)-C(4)	120.7(2)
C(5)-C(6)-C(1)	120.4(2)
N(8)-C(7)-C(1)	117.60(16)
N(8)-C(7)-C(16)	123.59(17)
C(1)-C(7)-C(16)	118.80(16)
N(8)-C(9)-C(10)	109.15(16)

N(8)-C(9)-C(9)#1	107.3(2)
C(10)-C(9)-C(9)#1	111.4(2)
C(15)-C(10)-C(11)	118.6(2)
C(15)-C(10)-C(9)	121.1(2)
C(11)-C(10)-C(9)	120.3(2)
C(12)-C(11)-C(10)	120.8(3)
C(13)-C(12)-C(11)	120.3(3)
C(12)-C(13)-C(14)	119.8(3)
C(13)-C(14)-C(15)	120.7(3)
C(10)-C(15)-C(14)	119.8(3)
C(21)-C(16)-C(17)	118.76(19)
C(21)-C(16)-C(7)	121.11(18)
C(17)-C(16)-C(7)	120.01(18)
C(18)-C(17)-C(16)	120.3(2)
C(19)-C(18)-C(17)	120.6(2)
C(18)-C(19)-C(20)	120.0(2)
C(19)-C(20)-C(21)	119.8(2)
C(20)-C(21)-C(16)	120.5(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **255**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(8)	34(1)	31(1)	33(1)	0(1)	1(1)	-4(1)
C(1)	27(1)	32(1)	34(1)	-2(1)	4(1)	1(1)
C(2)	41(1)	45(1)	39(1)	3(1)	-4(1)	-6(1)
C(3)	40(1)	50(1)	54(2)	-5(1)	-11(1)	-10(1)
C(4)	32(1)	42(1)	64(2)	0(1)	1(1)	-8(1)
C(5)	35(1)	42(1)	48(1)	6(1)	7(1)	-4(1)
C(6)	31(1)	41(1)	39(1)	-1(1)	4(1)	-4(1)
C(7)	28(1)	31(1)	29(1)	-1(1)	2(1)	4(1)
C(9)	37(1)	31(1)	29(1)	4(1)	1(1)	-8(1)
C(10)	37(1)	33(1)	39(1)	-8(1)	-2(1)	-5(1)
C(11)	46(2)	39(1)	50(1)	-2(1)	-3(1)	5(1)
C(12)	63(2)	47(2)	69(2)	-11(1)	-15(2)	16(1)
C(13)	49(2)	62(2)	92(2)	-30(2)	-13(2)	16(2)
C(14)	41(2)	77(2)	90(2)	-18(2)	15(2)	-6(2)
C(15)	44(2)	56(2)	65(2)	-5(1)	10(1)	-7(1)
C(16)	31(1)	32(1)	28(1)	-2(1)	-2(1)	-3(1)
C(17)	42(1)	41(1)	34(1)	1(1)	5(1)	4(1)
C(18)	51(2)	52(1)	37(1)	3(1)	13(1)	-4(1)
C(19)	67(2)	44(1)	34(1)	7(1)	2(1)	-12(1)
C(20)	55(2)	40(1)	45(1)	7(1)	-12(1)	2(1)
C(21)	38(1)	40(1)	37(1)	2(1)	-3(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **255**.

	x	y	z	U(eq)
H(2)	8093(19)	2342(18)	2813(14)	44(6)
H(3)	9640(20)	4000(20)	2889(16)	57(7)
H(4)	9920(20)	5230(20)	1524(14)	51(6)
H(5)	8618(19)	4783(17)	85(13)	36(5)
H(6)	7110(20)	3140(17)	-3(14)	41(6)
H(9)	4764(18)	-92(17)	979(13)	35(5)
H(11)	3930(20)	2040(20)	-940(15)	53(7)
H(12)	1830(30)	2960(20)	-1304(18)	76(8)
H(13)	50(30)	2390(30)	-388(19)	103(10)
H(14)	430(30)	930(20)	928(19)	84(9)
H(15)	2540(20)	80(20)	1285(17)	68(8)
H(17)	4476(19)	1719(18)	2504(13)	37(5)
H(18)	4050(20)	440(20)	3844(16)	66(7)
H(19)	5530(20)	-1125(19)	4344(16)	51(6)
H(20)	7490(20)	-1460(20)	3559(14)	51(6)
H(21)	7940(20)	-218(19)	2183(15)	52(6)

Table 6. Torsion angles [°] for **255**.

C(6)-C(1)-C(2)-C(3)	-0.9(3)
C(7)-C(1)-C(2)-C(3)	-179.03(19)
C(1)-C(2)-C(3)-C(4)	1.2(3)
C(2)-C(3)-C(4)-C(5)	-0.6(3)
C(3)-C(4)-C(5)-C(6)	-0.2(3)
C(4)-C(5)-C(6)-C(1)	0.5(3)
C(2)-C(1)-C(6)-C(5)	0.0(3)
C(7)-C(1)-C(6)-C(5)	178.21(18)
C(9)-N(8)-C(7)-C(1)	179.21(16)
C(9)-N(8)-C(7)-C(16)	-1.8(3)
C(2)-C(1)-C(7)-N(8)	179.75(19)
C(6)-C(1)-C(7)-N(8)	1.6(3)
C(2)-C(1)-C(7)-C(16)	0.7(3)
C(6)-C(1)-C(7)-C(16)	-177.45(18)
C(7)-N(8)-C(9)-C(10)	115.1(2)
C(7)-N(8)-C(9)-C(9)#1	-124.1(2)
N(8)-C(9)-C(10)-C(15)	-128.1(2)
C(9)#1-C(9)-C(10)-C(15)	113.6(3)
N(8)-C(9)-C(10)-C(11)	52.1(2)
C(9)#1-C(9)-C(10)-C(11)	-66.1(3)
C(15)-C(10)-C(11)-C(12)	-0.9(3)
C(9)-C(10)-C(11)-C(12)	178.9(2)
C(10)-C(11)-C(12)-C(13)	0.6(4)
C(11)-C(12)-C(13)-C(14)	0.1(4)
C(12)-C(13)-C(14)-C(15)	-0.6(4)
C(11)-C(10)-C(15)-C(14)	0.4(3)
C(9)-C(10)-C(15)-C(14)	-179.3(2)
C(13)-C(14)-C(15)-C(10)	0.3(4)
N(8)-C(7)-C(16)-C(21)	103.3(2)
C(1)-C(7)-C(16)-C(21)	-77.7(2)
N(8)-C(7)-C(16)-C(17)	-72.8(3)
C(1)-C(7)-C(16)-C(17)	106.2(2)
C(21)-C(16)-C(17)-C(18)	-1.4(3)
C(7)-C(16)-C(17)-C(18)	174.77(19)
C(16)-C(17)-C(18)-C(19)	0.3(3)
C(17)-C(18)-C(19)-C(20)	0.8(3)
C(18)-C(19)-C(20)-C(21)	-0.9(3)
C(19)-C(20)-C(21)-C(16)	-0.2(3)

C(17)-C(16)-C(21)-C(20)	1.4(3)
C(7)-C(16)-C(21)-C(20)	-174.79(18)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z

Table 1. Crystal data and structure refinement for **301.**

Empirical formula	C8 H10 O3	
Formula weight	154.16	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 6.4218(19) Å	α= 90°.
	b = 6.4487(13) Å	β= 94.03(3)°.
	c = 19.663(7) Å	γ = 90°.
Volume	812.3(4) $Å^3$	
Z	4	
Density (calculated)	1.261 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	328	
Crystal size	0.30 x 0.30 x 0.30 mm^3	
Theta range for data collection	3.28 to 25.00°.	
Index ranges	-7<=h<=7, 0<=k<=7, -23<=l<=23	
Reflections collected	2847	
Independent reflections	1426 [R(int) = 0.0272]	
Completeness to theta = 25.00°	99.7 %	
Absorption correction	None	
Max. and min. transmission	0.9717 and 0.9717	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1426 / 0 / 140	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1122	
R indices (all data)	R1 = 0.0666, wR2 = 0.1270	
Largest diff. peak and hole	0.159 and -0.093 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **301**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	13700(3)	23648(2)	18977(1)	89(1)
O(2)	13939(3)	25618(3)	18031(1)	86(1)
O(3)	16160(2)	26143(3)	18965(1)	87(1)
C(1)	17678(6)	22136(5)	18062(2)	104(1)
C(2)	16501(4)	23224(4)	18308(1)	73(1)
C(3)	15039(3)	24686(3)	18576(1)	56(1)
C(4)	12205(5)	25015(4)	19254(2)	81(1)
C(5)	12600(3)	27187(3)	19011(1)	59(1)
C(6)	14829(4)	27677(4)	19237(2)	80(1)
C(7)	12456(5)	27125(5)	18252(1)	86(1)
C(8)	11098(5)	28715(5)	19308(2)	93(1)

Table 3. Bond lengths [Å] and angles [°] for **301**.

O(1)-C(3)	1.381(2)
O(1)-C(4)	1.438(3)
O(2)-C(3)	1.378(2)
O(2)-C(7)	1.448(3)
O(3)-C(3)	1.382(2)
O(3)-C(6)	1.435(3)
C(1)-C(2)	1.162(4)
C(2)-C(3)	1.454(3)
C(4)-C(5)	1.507(3)
C(5)-C(7)	1.490(3)
C(5)-C(6)	1.502(3)
C(5)-C(8)	1.523(3)
C(3)-O(1)-C(4)	112.27(16)
C(3)-O(2)-C(7)	111.85(15)
C(3)-O(3)-C(6)	112.01(16)
C(1)-C(2)-C(3)	175.9(3)
O(2)-C(3)-O(1)	110.44(17)
O(2)-C(3)-O(3)	110.58(18)
O(1)-C(3)-O(3)	109.52(16)
O(2)-C(3)-C(2)	108.10(15)
O(1)-C(3)-C(2)	109.66(17)
O(3)-C(3)-C(2)	108.48(16)
O(1)-C(4)-C(5)	108.54(18)
C(7)-C(5)-C(6)	107.0(2)
C(7)-C(5)-C(4)	107.0(2)
C(6)-C(5)-C(4)	106.2(2)
C(7)-C(5)-C(8)	113.9(2)
C(6)-C(5)-C(8)	111.5(2)
C(4)-C(5)-C(8)	110.8(2)
O(3)-C(6)-C(5)	108.97(18)
O(2)-C(7)-C(5)	108.82(18)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **301**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	108(1)	55(1)	110(1)	16(1)	50(1)	10(1)
O(2)	103(1)	106(1)	47(1)	6(1)	-3(1)	30(1)
O(3)	56(1)	95(1)	108(1)	-43(1)	-9(1)	6(1)
C(1)	110(2)	118(2)	84(2)	-20(2)	11(2)	36(2)
C(2)	83(2)	79(1)	58(1)	-8(1)	6(1)	12(1)
C(3)	60(1)	61(1)	45(1)	1(1)	1(1)	0(1)
C(4)	80(2)	71(2)	95(2)	11(1)	30(1)	4(1)
C(5)	57(1)	54(1)	67(1)	2(1)	4(1)	2(1)
C(6)	66(1)	71(2)	100(2)	-24(1)	-1(1)	2(1)
C(7)	91(2)	94(2)	72(2)	14(1)	-7(1)	26(2)
C(8)	75(2)	75(2)	129(3)	-9(2)	14(2)	15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **301**.

	x	y	z	U(eq)
H(1)	18600(60)	21460(50)	17894(18)	139(14)
H(4A)	12350(40)	24900(50)	19766(16)	115(9)
H(4B)	10860(50)	24600(50)	19055(15)	121(11)
H(6A)	15060(50)	27690(50)	19752(18)	130(11)
H(6B)	15180(50)	29010(50)	19057(14)	110(10)
H(7A)	12770(50)	28410(50)	18035(16)	126(11)
H(7B)	11060(50)	26730(50)	18045(15)	117(10)
H(8A)	11350(50)	30090(60)	19134(14)	113(10)
H(8B)	9720(60)	28340(50)	19133(15)	117(10)
H(8C)	11280(70)	28700(60)	19850(20)	181(17)

Table 6. Torsion angles [°] for **301**

C(7)-O(2)-C(3)-O(1)	60.7(3)
C(7)-O(2)-C(3)-O(3)	-60.7(2)
C(7)-O(2)-C(3)-C(2)	-179.3(2)
C(4)-O(1)-C(3)-O(2)	-60.7(3)
C(4)-O(1)-C(3)-O(3)	61.3(3)
C(4)-O(1)-C(3)-C(2)	-179.7(2)
C(6)-O(3)-C(3)-O(2)	60.3(2)
C(6)-O(3)-C(3)-O(1)	-61.6(2)
C(6)-O(3)-C(3)-C(2)	178.7(2)
C(1)-C(2)-C(3)-O(2)	32(4)
C(1)-C(2)-C(3)-O(1)	153(4)
C(1)-C(2)-C(3)-O(3)	-88(4)
C(3)-O(1)-C(4)-C(5)	-0.1(3)
O(1)-C(4)-C(5)-C(7)	57.0(3)
O(1)-C(4)-C(5)-C(6)	-57.0(3)
O(1)-C(4)-C(5)-C(8)	-178.3(2)
C(3)-O(3)-C(6)-C(5)	0.4(3)
C(7)-C(5)-C(6)-O(3)	-57.2(3)
C(4)-C(5)-C(6)-O(3)	56.9(3)
C(8)-C(5)-C(6)-O(3)	177.7(2)
C(3)-O(2)-C(7)-C(5)	0.1(3)
C(6)-C(5)-C(7)-O(2)	56.6(3)
C(4)-C(5)-C(7)-O(2)	-56.9(3)
C(8)-C(5)-C(7)-O(2)	-179.7(2)

Symmetry transformations used to generate equivalent atoms:

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